THE MODE OF ACTION OF ANAESTHETICS

PRINTED IN GREAT BRITAIN
AT THE CENTRAL PRESS (ABERDEEN) LTD.
ABERDEEN

THE MODE *of* ACTION *of* ANAESTHETICS

BY

T. A. B. HARRIS
M.B., B.S., D.A., F.F.A.R.C.S.
Anæsthetist to Guy's Hospital and to St. Peter's Hospital for Stone

EDINBURGH
E. & S. LIVINGSTONE LTD.
16 & 17 TEVIOT PLACE
1951

With this conception of the mode of action of narcotics on unicellular organisms, one may consider the action of those narcotics which are suitable for use in clinical practice. It can be assumed that the fixation of anæsthetics by and their subsequent action on, the individual cells of a heterogeneous cell-system such as Man is the same as in unicellular organisms. This implies that the response of Man to anæsthetics can be interpreted in terms of the sequence of the absorption of an effective concentration of the anæsthetic by each of the several organs and areas of functional activity of his body. Viewed in this light, the sequence of absorption of an effective concentration of the anæsthetics in common clinical use and in turn the character of their action in Man, is seen to follow a definite pattern which is determined by the physical properties of the given anæsthetic. Anæsthetics with an oil/water partition coefficient of more than unity and less than about 14, produce the standard safe sequence of response in all circumstances and with these drugs, overdose produces death by secondary cardiac failure. Those anæsthetics whose oil/water partition coefficient is high produce the standard sequence of response when a graduated method of induction is achieved but when overpressure is used, primary cardiac failure may occur. The control of the absorption of anæsthetics by the body in the safe standard sequence is then discussed in terms of the physical properties of particular anæsthetics and the clinical signs of anæsthesia.

An effort is then made to wean the anæsthetist from the empiricism of control based solely on the clinical signs of anæsthesia, and to substitute a picture of the release phenomena which occur when the functional activity of the brain is depressed level by level during blood-borne anæsthesia. This essay to chart the sequence of depression of the several brain nuclei during blood-borne anæsthesia is followed by an examination of the factors which act to produce loss of muscle tone during anæsthesia and this logically leads to a consideration of the mode of action of

d-tubo-curarine chloride. This section ends with speculations concerning cholinergic transmission at central synapses and its relation to the problems of blood-borne anæsthesia.

The story ends with a review of the influence of blood-borne anæsthetics on the metabolism of the body taken as a whole and on its several organs and systems.

The writer's approach to these several problems has been greatly influenced by the works of A. J. Clark and J. H. Quastel. He has received the utmost consideration from his surgical colleagues and help and guidance from the Directors of the several Departments of Guy's Hospital Medical School. It must be emphasized, however, that while the help of these friends was indispensible, they are not responsible for the conclusions drawn by the writer or the opinions expressed by him. Perhaps the writer has been too ready to accept logical probabilities based on accepted facts in order to complete the story. This is deliberate and is done with the object of stimulating interest and research.

T. A. B. HARRIS.

GUY'S HOSPITAL,
LONDON, 1951.

ACKNOWLEDGMENTS

It is a real pleasure to be able to thank Professor W. P. Spurrel who has advised me with much of the manuscript of Part 2 and the neurological section of Part 3. Amongst my friends and colleagues who have helped me, I am indebted to the Directors of each of the several Departments of Guy's Hospital Medical School and to P. M. Bennett of the Royal Veterinary College. I am particularly grateful to Dr. A. W. Hind for reading the book in proof and for his valuable criticisms and suggestions. I wish to thank Mr. J. F. Dudley of the Guy's Hospital Dental School who made the microphotographs shown in Figure 12, and the Staff of Guy's Hospital Illustrating Department who were responsible for all other figures and diagrams. Part of the cost of the temperature curves shown in Chapter 26 was met from a grant made to me by the British Medical Research Council.

The author acknowledges with grateful thanks the permission granted by the authors, editors and publishers to use the following material:—

BODANSKY: "Introduction to Physiological Chemistry" 3rd ed. (1934) p. 609. Wiley, New York.

BURNS: "An Introduction to Biophysics" (1921) p. 348. Churchill, London.

CLARK (adapted from Ravenos): *Jour. Physiol.* (1936-37) 88, 3. Cambridge University Press, London.

GORODISSKY: *Biochem. Zeit.* (1925) 164, 446. Springer-Verlag, Heidelberg.

GOLDSCHMIDT *et al.*: *Jour. Amer. Med. Assoc.* (1934) 102, 21. Chicago.

HAGGARD: *Jour. Biol. Chem.* (1924) 59, 775 and 776, Tables 1, 2 and 3. The Williams & Wilkins Co., Baltimore.

HANSEN: "Zur Theorie der Narkose" (1925). Olaf Norlis Forlag, Oslo.

HANSEN: *Skand. Arch. f. Physiol.* (1925). 315, 46. Norstedt & Soner, Stockholm.

KING: *Surg. Gynec. & Obstets.* 56, 43, Tables 6 and 9. Chicago.

KOCKMAN: "Handbuch der Experimentallen Pharmakologie" Table 16. Springer-Verlag, Heidelberg.

KUNTZ, BENNETT and SHAPIRO. *Jour. Amer. Med. Assoc.* (1936) 106, 434 Chicago.

MCCOLLUM *Jour. Pharmaceut. & Exper. Therapy* (1930) 46, 609. The Williams & Wilkins Co., Baltimore.

MACLEOD. "Physiology and Biochemistry in Modern Medicine" 6th Ed. p. 170. Kimpton, London.
MEYERHOFF *Pflugrs Arch.* (1914) 157, 263. Springer-Verlag, Heidelberg.
MILLER, Ross, and WHIPPLE *Amer. J. Med. Sci.* (1940) 200, 741, Table I.
NICLOUX *Comp. Rend. Soc Biol.* (1934) 115, 1284. Masson & Cie, Paris.
NICLOUX· *Comt. Rend. d l' Acad d. Sciences* (1907) 144, 341. Gauthier-Villars, Paris.
PRINGLE *Brit. Med. Jour.* (1905) 2, 542. British Medical Association, London.
QUASTEL *Proc. Roy Soc.* (1932) 3B, 112, 71 and 74. The Royal Society, London
RAYNER *Proc Instit. Elect Engineers* (1938) 83, 170. Institution of Electrical Engineers, London
ROBERTSON *Biochem. Jour.* (1933) 27, 84, Table I. Cambridge University Press, London.
TABERN *Jour. Amer. Chem. Soc.* (1933) 55, 328. American Chemical Society, New York.
TOWNEND and CHAMBERLAIN· *Proc. Roy Soc.* A. 894, 154, 415, Figs. 1 and 3. The Royal Society, London
WARBURG *Biochem. Zeitschr.* (1921) 119, 145, Table IV. Springer-Verlag, Heidelberg.
WOOLF *Assoc for Research in Nerv. and Ment. Dis.* Vol. 18 (1937) p. 51, Fig 22 Association for Research in Nervous and Mental Disease, New York.
WRIGHT "Applied Physiology" 7th Ed. p. 502. Oxford University Press, London

CONTENTS

PART THREE

THE CO-RELATION OF THE LEVEL OF ANÆSTHETIC DEPRESSION OF THE NERVOUS SYSTEM WITH ANÆSTHETIC SLEEP; LOSS OF SENSATION AND LOSS OF MUSCLE MOVEMENT AND MUSCLE TONE

PART FOUR

METABOLISM DURING ANÆSTHESIA

PART ONE

NARCOTICS



INTRODUCTION

NARCOSIS, or anæsthesia, has been defined as the controlled freely reversible depression of the normal response of the whole or part of the body to stimuli, and this clinical state is produced by chemical agents called narcotics or anæsthetics.

Narcosis means a state of numbness or paralysis. As the biologists understand the term, narcosis may be produced by a variety of physical and chemical agents, such as heat, cold, electricity, oxygen lack, some ions and some chemical compounds. In pharmacology, however, the term "narcosis" has a more precise meaning, namely the temporary and reversible diminution or abolition of the normal autonomic activity of cells, by means of specific chemical substances known as narcotics.

Anæsthesia means the abolition of conscious sensation, and perforce should be applied exclusively to the higher forms of life. It is used in clinical medicine to describe the controlled, reversible depression of the functional activity of the central nervous system of the higher forms of life, and is used also to describe the local reversible depression of the functional activity of peripheral nerves.

By common usage, these two terms, narcosis and anæsthesia, are frequently employed as synonyms. This convention is not justified, for many narcotics that can depress the autonomic activity of unicellular organisms in a reversible manner are either inert when used as anæsthetics in the higher forms of life, or are unsuitable for use in clinical anæsthetic practice because they have deleterious side-actions.

In the discussion which follows, a distinction will be drawn between these two terms. *Narcosis* will be used to describe the reversible depression of the autonomic activity of cells which is produced by narcotic drugs. *Anæsthesia*, on the other hand, will be used to describe the controlled, freely reversible depression of the functional activity of the central nervous system of the higher forms of life, produced as an aid to surgery by anæsthetic drugs. *Anæsthesia* will also be used to describe the local reversible depression of the functional activity of peripheral nerves produced by local anæsthetic drugs in surgical practice.

CHAPTER I

THE CONCENTRATION-ACTION RELATION OF NARCOTICS

THE biological response of cells and enzymes to a given concentration of a narcotic may be measured experimentally, and, if the amount of action produced by a series of concentrations is measured, it is possible to construct a concentration-action curve of the response of the cell, or enzyme, to the narcotic.

The interpretation of such curves is a matter of some difficulty, for the following reasons. The range of experimental observation is limited by the fact that the activity of living cells is maintained only within a narrow range of physio-chemical conditions, if these conditions are not preserved the cell dies. On this account, and also because of the secondary effects which may occur when the concentration of the narcotic is increased beyond certain limits, the upper limit of action cannot be accurately determined in many cases.

For example, the depressing effect of a potent narcotic such as chloroform on most isolated tissue can be accurately measured from 0 to 100%, but, with a weak narcotic such as alcohol, when the upper limit of concentration is reached, the concentration of alcohol is so great that gross changes are produced in the physical properties of the perfusion fluid; the biological response measured at the upper limit of concentration is probably a combination of narcotic action and other effects. Apart from such confusing side-actions, it is seldom possible to obtain data accurate to within 10% over the full range, judged by the standards of the physical chemist such data would be considered far too inaccurate for mathematical analysis

Again, the type of curve obtained depends essentially upon the type of biological action measured. Figure 1, which represents the concentration-action relation of ethyl urethane on sea-urchin's eggs, illustrates this point.

Curve A shows the effect of different concentrations of ethyl urethane in inhibiting fertilization. The result is a sigmoid curve characteristic of an "all-or-none" reaction, for this is a measure of the individual susceptibility of the members of this cell population to the action of the narcotic. Curve B shows the effect of

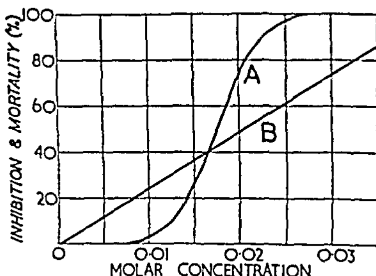


FIGURE 1.
Concentration-action curves of ethyl urethane acting on sea-urchins eggs

different concentrations of the narcotic in reducing the oxygen consumption of the cells. This is a typical "graded" reaction, and a linear relation is seen to exist between the concentration of the narcotic and the diminution of oxygen consumption by the cells. The objection has been made that the depression of cell oxidation should not be employed as a measure of narcotic effect; but conclusions will be reached in this discussion indicating that this is the most nearly relevant index that could be employed.

It must be realized, too, that there is a minimal threshold concentration below which a given narcotic *will not* produce its characteristic response on particular living cells and enzymes, and that many narcotics produce their maximal biological response before the cell is fully saturated.

Finally, it must be emphasized that a concentration-action curve is the summation of at least three processes— the uptake of the narcotic by the cell, the fixation of the narcotic by the cell, and the biological response of the cell to the mass of narcotic fixed.

Figure 2 and Figure 3 illustrate respectively the concentration/action relation of ethyl alcohol on the inhibition of the mechanical

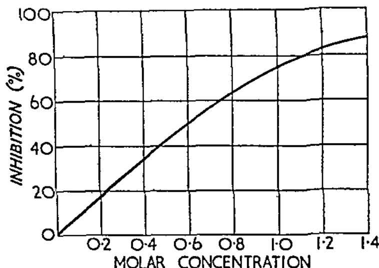


FIGURE 2.
Concentration-action curve of ethyl alcohol on frog's isolated heart.

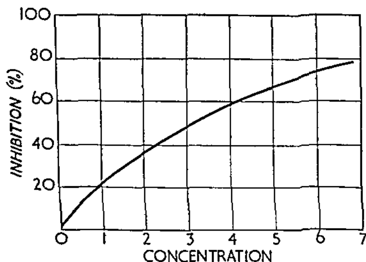


FIGURE 3
Concentration-action curve of ethyl alcohol on the enzyme invertase.

response of a frog's ventricle and the inhibition of the enzyme invertase. In each instance the curve is linear, and a graded response is produced, this indicates that the amount of inhibition

in the cell and in the enzyme is directly proportional to the concentration of ethyl alcohol in the extracellular fluid in contact with the cell or enzyme. The same type of graded response is seen in Curve B of Figure 1. This graded response commonly obtains with soluble narcotics low in molecular weight and potency.

Storm van Leeuwen and Le Heux (1919) with morphia, and Rona and Ammon (1926) with a variety of alkaloids, have shown that, in general, the concentration/action relation of narcotic alkaloids is exponential in character. The biological response of cells and enzymes to this type of narcotic is, therefore, a graded one, but the amount of action produced is proportional to the logarithm of the concentration of the narcotic in the extracellular fluid in contact with the cell or enzyme. This is the common form of relation found with relatively insoluble narcotics, high in molecular weight and potency, and acting in high dilutions.

Two conclusions can be drawn. *First*, that narcotics act in a graded manner on cells and enzymes, the amount of action varying, sometimes directly and sometimes logarithmically, as the concentration of the narcotic in the extracellular fluid with which the cell is in contact; this applies alike to the cells of a population of unicellular organisms and to the cells of a heterogeneous cell system such as Man. *Second*, that when more than one narcotic is brought into contact with a living cell, the response produced is the sum of the amount of action that each would produce singly in contact with the cell. Winterstein (1926) summarises the general result as follows: "Substances which belong to the same pharmacological group, when combined, frequently produce an additive effect."

These two conclusions are all that the empiric anæsthetist requires in proceeding to the later discussion (in Part Two), which deals with how the concentration of anæsthetics in the extracellular fluid of a heterogeneous cell system can be controlled. Should the anæsthetist be interested in how anæsthetics, having been concentrated in extracellular fluid, act on the cells of a heterogeneous cell system such as Man—and the author believes that this aspect is necessary to understanding fully the problems of anæsthesia in clinical practice—then he should examine the data set out in the remaining chapters of Part One.

Figure 2 and Figure 3 illustrate respectively the concentration/action relation of ethyl alcohol on the inhibition of the mechanical

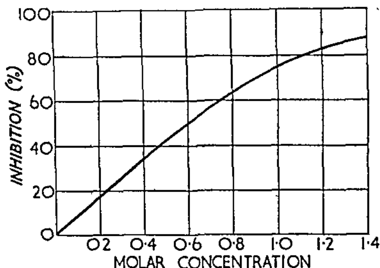


FIGURE 2

Concentration-action curve of ethyl alcohol on frog's isolated heart.

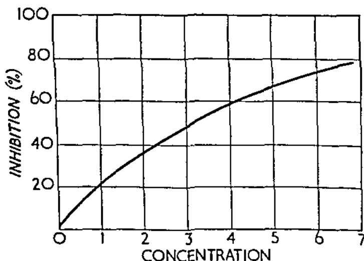


FIGURE 3.

Concentration-action curve of ethyl alcohol on the enzyme invertase.

response of a frog's ventricle and the inhibition of the enzyme invertase. In each instance the curve is linear, and a graded response is produced; this indicates that the amount of inhibition

TABLE 1 (Cont.).

SUBSTANCE	FORMULA	B.P. °C.	STATE	ANÆSTHETIC POTENCY
Halogen Substitution Products of Ethylene (Unsaturated)				
Dichloroethylene	$C_2H_2Cl_2$	55·0	Liquid	Potent Narcotics
Trichloroethylene	C_2HCl_3	87·1	Liquid	.. ..
Perchloroethylene	C_2Cl_4	119 0	Liquid	.. ..
Amino Substitution Products				
Nitromethane	CH_3NO_2	100 0	Liquid	Inert narcotically
Nitroethane	$C_2H_5NO_2$	114·0	Liquid	.. ..
HYDROXYL SUBSTITUTION PRODUCTS: THE ALCOHOLS				
Primary Alcohols (Saturated)				
Methyl Alcohol	CH_3OH	66·0	Liquid	Weak narcotic
Ethyl Alcohol	C_2H_5OH	78·5	Liquid	Hypnotic
Propyl Alcohol	C_3H_7OH	97 5	Liquid	..
Butyl Alcohol	C_4H_9OH	117·0	Liquid	..
Amyl Alcohol	$C_5H_{11}OH$	137·0	Liquid	..
Tertiary Alcohols (Saturated)				
Amylene Hydrate	$(CH_3)_2C.C_2H_5OH$	102 0	Liquid	Fairly potent Anæsthetic
Unsaturated Alcohols				
Vinyl Alcohol	CH_2CHOH		Unstable	Weak hypnotic
Halogen Substitution Products of the Alcohols				
Avertin	CBr_3CH_2OH		Solid	
Trichlorethyl Alcohol	$C.Cl_3CH_2OH$	151·	Liquid	Basal Anæsthetic
DERIVATIVES OF THE ALCOHOLS				
The Ethers				
Di-methyl Ether	CH_3OCH_3	−21·0	Gas	Fairly potent
Di-ethyl Ether	$C_2H_5OC_2H_5$	34 0	Liquid	Potent Anæsthetic
Di-Propyl Ether	$C_3H_7OC_3H_7$	86 0	Liquid	.. ..
Di-vinyl Ether	$C_2H_3OC_2H_3$	28·0	Liquid	.. ..

TABLE I.

NARCOTICS

SUBSTANCE	FORMULA	B P. °C	STATE	ANÆSTHETIC POTENCY
INORGANIC OXIDES				
Carbon Dioxide	CO_2		Gas	Inert
Nitrous Oxide	N_2O	- 87·9	Gas	Weak anæsthetic
ORGANIC SUBSTANCES				
SATURATED ALIPHATIC HYDROCARBONS : THE PARAFFIN SERIES				
Methane	CH_4	- 160·0	Gas	Very weak
Ethane	C_2H_6	- 85·4	Gas	
Propane	C_3H_8	- 37·0	Gas	
Butane	C_4H_{10}	1·0	Gas	
Pentane	C_5H_{12}	37·0	Liquid	Fairly potent anæsthetic
Hexane	C_6H_{14}	69·0	Liquid	
Heptane	C_7H_{16}	98·0	Liquid	
Octane	C_8H_{18}	124·0	Liquid	
Nonane	C_9H_{20}	148·0	Liquid	
Decane	$C_{10}H_{22}$	168·0	Liquid	Inert
UNSATURATED ALIPHATIC HYDROCARBONS : THE OLEFINE SERIES				
Ethylene	C_2H_4	- 103·0	Gas	Fairly potent anæsthetic
Propylene	C_3H_6	- 37·0	Gas	
Butylene	C_4H_8	- 5	Gas	
Amylene	C_5H_{10}	35·0	Liquid	Potent
UNSATURATED ALIPHATIC HYDROCARBONS : THE ACETYLENE SERIES				
Acetylene	C_2H_2	- 81·5	Gas	Fairly potent anæsthetic
Allylene	C_3H_4	- 23·5	Gas	
Crotonylene	C_4H_6	27·5	Liquid	Potent
HALOGEN SUBSTITUTION PRODUCTS OF THE ALIPHATIC HYDROCARBONS				
Halogen Substitution Products of Methane (Saturated)				
Methyl Chloride	CH_3Cl	- 24·0	Gas	Potent
Methylene Dichloride	CH_2Cl_2	41·0	Liquid	
Trichloromethane	$CHCl_3$	61·2	Liquid	Very potent
Tetrachloromethane	CCl_4	76·7	Liquid	Less potent
Halogen Substitution Products of Ethane (Saturated)				
Ethyl Chloride	C_2H_5Cl	12·5	Gas	Potent anæsthetic
Ethylene Dichloride	$C_2H_4Cl_2$	85·0	Liquid	Less potent

TABLE 1 (Cont.).

SUBSTANCE	FORMULA	STATE	ANÆSTHETIC POTENCY
Ethereal Salts			
Methyl Acetate	$CH_3CO_2CH_3$	Liquid	Weak Narcotic
Ethyl Acetate	$C_2H_5CO_2C_2H_5$	Liquid	,, ,,
Amides			
Acetamide	CH_3CONH_2	Solid	Inert
Urea	$CO(NH_2)_2$	Solid	,,
Carbamic Acid Derivatives			
Ethyl Urethane	$CO.NH_2OC_2H_5$	Solid	Weak Hypnotic
SUBSTITUTION PRODUCTS OF UREA			
Amino Derivatives of Urea			
Di-Acetyl Urea	$(NH.OC.CH_3)_2CO.$	Solid	Weak Hypnotics
Carbromal	$(C_2H_5)_2Br.C.NH.OC\ NH_2CO.$	Solid	,, ,,
ALICYCLIC HYDROCARBONS			
Cyclopropane	C_3H_6	Gas	Potent Anæsthetic
Cyclopropyl-Methyl Ether	$C_3H_5CHO.CH_3.$	Liquid	Potent Anæsthetics but irritants
Cyclopropyl-Ethyl Ether	$C_3H_4.CHO.C_2H_5$	Liquid	Potent Anæsthetics but irritants
HETEROCYCLIC COMPOUNDS			
Cyclic Ureids: The Barbiturates			
Barbitone	$OC.(NHOC)_2C.(C_2H_5)_2$	Solid	Hypnotics
Sod. Barbitone	$NaO.NHOC.NOC.C(C_2H_5)_2$	Solid	,,
Luminal	Phenyl ethyl barbiturate	Solid	,,
Amytal	Iso amyl ethyl barbiturate	Solid	,,
Nembutal	Ethyl methyl butyl barbiturate	Solid	,,
Evipan	N. methyl c.c. cyclo. hexanyl barbiturate.	Solid	Potent Anæsthetic
The Thio-Barbiturates			
Pentothal	Ethyl (1 methyl butyl) thio barbiturate	Solid	Potent Anæsthetic

TABLE 1 (Cont.).

SUBSTANCE	FORMULA	STATE	ANÆSTHETIC POTENCY
THE SULPHUR DERIVATIVES OF ALCOHOL			
Ethyl Mercaptol	C_2H_5SH	Liquid	Weak Hypnotic
The Thio-Ethers			
Acetone Ethyl Mercaptol	$(CH_3)_2C.(SC_2H_5)_2$	Solid	Weak Hypnotic
Di-Methyl Sulphones			
	$(CH_3)_2C.(SO_2CH_3)_2$	Solid	Weak Hypnotics
	$CH_3C_2H_5C.(SO_2CH_3)_2$	Solid	,, ,,
	$(C_2H_5)_2C(SO_2CH_3)_2$	Solid	,, ,,
Di-Ethyl Sulphones			
Sulphonal	$(CH_3)_2C(SO_2C_2H_5)_2$	Solid	Effective Hypnotics
Trional	$CH_3C_2H_5C(SO_2C_2H_5)_2$	Solid	,, ,,
Tetranol	$(C_2H_5)_2C(SO_2C_2H_5)_2$	Solid	,, ,,
Ketones			
Di-Methyl Ketone	$(CH_3)_2CO.$	Liquid	Potent Narcotics
Methyl-Ethyl Ketone	$CH_3CO\ C_2H_5$	Liquid	,, ,,
OXIDATION PRODUCTS OF THE ALCOHOLS			
Aldehydes			
Formaldehyde	CH_2O	Gas	Irritants
Acetaldehyde	$C_2H_4O.$	Liquid	,,
Propylaldehyde	$C_3H_6.O$	Liquid	,,
Paraldehyde	$(C_2H_4O)_3$	Liquid	Basal Anæsthetic
SUBSTITUTED ALDEHYDES			
Halogen Aldehydes			
Chloral Hydrate	$C\ Cl_3CHO.$	Solid	Hypnotic
OXIDATION PRODUCTS OF THE ALDEHYDES			
Organic Acids			
Acetic Acid	$CH_3COOH.$	Liquid	Inert
DERIVATIVES OF ORGANIC ACIDS			
Esters			
Methyl Nitrate	CH_3NO_3	Liquid	Inert
Ethyl Nitrate	$C_2H_5NO_3$	Liquid	,,
Ethyl Nitrite	$C_2H_5NO_2$	Gas	,,

CHAPTER II

THE CHEMICAL CONSTITUTION OF NARCOTICS AND ITS RELATION TO PHARMACOLOGICAL ACTION

PHARMACOLOGICAL agents, excepting only carcinogens and mutagens, do not create new functions in tissue cells: they only modify the existing functions of the cells. A narcotic drug is no exception to this rule, and it must possess two essential properties if it is to produce its characteristic biological response on living cells. It must be capable of uniting with cell protoplasm, and having been fixed must then be capable of modifying cell function. These two essential attributes—the power to combine with the tissue cell and the ability to modify cell function—may be combined in the same chemical group of the molecular constitution of the drug, or each may be a separate entity, one chemical group affecting drug fixation, and another being responsible for the pharmacological action produced.

It is found, moreover, that the secondary actions (side actions) of a narcotic may be attributed to a particular radical, or group of radicals, in the molecule of the narcotic. For example, in chloroform, whose dominant action is narcosis, the number of chlorine atoms present in its molecule may be held responsible, not only for its narcotic potency, but also for the deleterious side-actions which this drug unfortunately possesses.

The influence of chemical radicals and side-chains in the molecular constitution of a narcotic drug is clearly of the greatest importance; and the substitution or the addition of particular chemical radicals or groups may modify decisively, not only the pharmacological action but also the physical properties of a narcotic drug. At this juncture, pharmacological properties are the primary consideration, and certain *generalizations concerning* the empiric relationship between chemical constitution and narcotic action may be made which are both instructive and interesting.

TABLE 1 (Cont.).

Substance	Formula	State	Anæsthetic Potency
Aromatic Compounds			
Benzene	C_6H_6	Liquid	Narcotics but
Toluene	$C_6H_5CH_3$	Liquid	Convulsants
Benzoic Acid	C_6H_5COOH.	Solid	Inert
Narcotic Alkaloids and Allied Substances			
Atropine	$C_{17}H_{23}O_3N$	Solid	Inert
Scopolamine	$C_{17}H_{21}O_4N$.	Solid	Hypnotic
Morphia	$C_{17}H_{19}O_3N$	Solid	Hypnotic
Cocaine	$C_{17}H_{22}O_4N$	Solid	Local Anæsthetics
Alpha Cocaine	$C_{17}H_{22}O_4N$.	Solid	,, ,,
Alpha Eucaine	$C_{19}H_{28}O_4N$.	Solid	,, ,,
Beta Eucaine	$C_{15}H_{22}O_2N$.	Solid	,, ,,
Stovaine	$C_{14}H_{22}O_2N$.	Solid	,, ,,
Alypine	$C_{16}H_{26}O_2N_2$	Solid	,, ,,
Procaine	$C_{13}H_{20}O_2N_2$	Solid	,, ,,
Pantocaine	$C_{15}H_{24}O_2N_2$	Solid	,, ,,
Orthoform	$C_8H_{12}O_3N$	Solid	,, ,,
Anesthesine	$C_9H_{13}O_2N$.	Solid	,, ,,
Nupercaine	$C_{20}H_{29}O_2N_3H.Cl$.	Solid	,, ,,

REFERENCES

1. LEEUWEN, W STORM VAN, and LE HEUX, J. W. (1919). *Pflüg. ges Physiol* **177**, 250
2. RONA P., and AMMON, R (1936) *Biochem Z.* **181**, 49.
3. WINTERSTEIN, H (1926). "Die Narkose," Julius Springer, Berlin.

atoms, di-chlor-ethane is a saturated hydrocarbon, and is more stable than ethylene. In the same way, the corresponding paraffin, ethane, is a saturated compound, and is more stable than ethylene.

The dominant pharmacological action of the members of the Olefin series is narcosis, and the series obeys the law of homologous series. Table 1. shows the relative potency of the first four members and, because it is an unsaturated series, each member is more potent than the corresponding member of the paraffin series. Ethylene, which has been extensively used as an anæsthetic, has no deleterious side-actions, but the higher members of the series produce cardiac arrythmias.

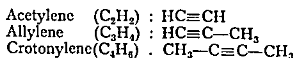
The members of the Acetylene Series of hydrocarbons are even less saturated than those of the Olefin series. The structural formula of the first member of the series, *acetylene*, shows that it is a symmetrical unsaturated hydrocarbon, and, in this instance, the tetravalent carbon atoms are linked by a triple bond.



$$H{-}C{\equiv}C{-}H.$$

As with the preceding series of hydrocarbons, an homologous series is built up by the substitution of a methyl radical for an hydrogen atom of the preceding member, and the molecular constitution of the members of this series increases in arithmetical progression by the term CH_2.

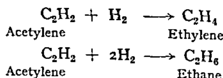
Thus:



Acetylene (C_2H_2) : $HC{\equiv}CH$
Allylene (C_3H_4) : $HC{\equiv}C{-}CH_3$
Crotonylene(C_4H_6) . $CH_3{-}C{\equiv}C{-}CH_3$

Just as ethylene readily takes up by addition two monovalent atoms because it contains two unsaturated carbon bonds, so also acetylene, which has four unsaturated carbon bonds, takes up by addition, either two univalent atoms to form a less saturated compound, or it takes up four monovalent atoms to form a saturated compound.

Thus:

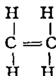


$$\underset{\text{Acetylene}}{C_2H_2} + H_2 \longrightarrow \underset{\text{Ethylene}}{C_2H_4}$$

$$\underset{\text{Acetylene}}{C_2H_2} + 2H_2 \longrightarrow \underset{\text{Ethane}}{C_2H_6}$$

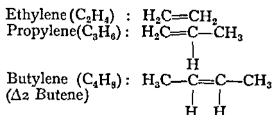
nervous system, which becomes more powerful with each successive increase in the molecular weight of the members of the series. The members of the paraffin series, from $C_{16}H_{34}$ onwards, are solids at body temperature.

The Olefin series of hydrocarbons are unsaturated compounds. The structural formula of the first member of this series, *ethylene* (C_2H_4), shows that it is a symmetrical unsaturated hydrocarbon, *for it is seen that the tetravalent carbon atoms are linked with a* double bond:



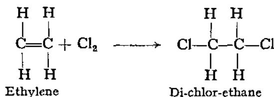
The olefin series is built up, member by member, by the substitution of a methyl radical for an hydrogen atom of the preceding member, and the molecular constitution of each successive member thus increases in arithmetical progression by the term CH_2.

Thus·



Because of this double bond, the members of the Olefin series are less stable than the corresponding members of the saturated paraffin series, and this instability is characterised by their ability *to form addition compounds by taking up directly two, but only* two, monovalent radicals.

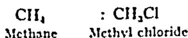
Thus:



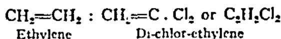
Since this process of addition saturates the tetravalent carbon

The halogen derivatives relevant to this discussion (listed in Table 1) in the main consist, therefore, of chlorine compounds of two saturated hydrocarbons, *methane* and *ethane*, and of the unsaturated hydrocarbon, *ethylene*.

Chlorinated hydrocarbons are formed by the substitution of a univalent chlorine atom for an hydrogen atom of a hydrocarbon, or the addition of a chlorine atom to an unsaturated hydrocarbon. Thus:







In each instance, when this substitution is continued, an homologous series of chlorinated hydrocarbons is built up, as shown in Table 1. The methyl and ethyl series, being saturated compounds, are more stable than the ethylene series, which are unsaturated, and all are relatively more active chemically than the corresponding hydrocarbon.

In each of these three series of chlorine substitution products, the hydrocarbon nucleus retains its influence upon the narcotic potency of the compounds; di-chlor-ethylene ($C_2H_2Cl_2$) is a more potent narcotic than the ethane substitution product, di-chlor-ethane ($C_2H_4Cl_2$), and this compound is in turn more potent than the methane derivative, methylene di-chloride (CH_2Cl_2).

The presence of chlorine in these compounds is, however, responsible for an increase in narcotic potency relative to the parent hydrocarbon, for methyl chloride is a more potent narcotic than methane, and ethyl chloride is more potent than ethane. It is found, moreover, that in a homologous series of chlorine substitution products narcotic potency increases with each additional chlorine atom substituted or added. When, however, chlorine

The dominant pharmacological action of the members of the Acetylene series of hydrocarbons is narcosis, and they obey the law of homologous series. The members of this series are more potent narcotics than the corresponding members of the Olefin series, and this is attributed to the fact that they are less saturated compounds. Acetylene is the only member of clinical importance. It has been used extensively in Germany, and its potency lies midway between that of ethylene and propylene.

This brief comparison of the three series of aliphatic hydrocarbons indicates that the similarity of their molecular constitution is responsible for a common dominant pharmacological action, narcosis In each series, the substitution of a methyl radical for an hydrogen atom results in an increase in the narcotic potency of the compound formed by this substitution, and in each series the narcotic potency increases as the carbon chain of the individual member increases in length. When the three series are compared, the narcotic potency of the corresponding members of each series increases as the molecule becomes progressively less saturated.

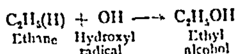
The compounds discussed above have been formed mainly by the substitution of a methyl radical. It is now proposed to ascertain the effect of substituting or adding radicals other than methyl on the narcotic potency of the aliphatic hydrocarbons.

Substitution Products of the Aliphatic Hydrocarbons

The Halogen Substitution Products. The substitution of one of the halogens (chlorine, bromine, or iodine), for the hydrogen atom of an aliphatic hydrocarbon is readily accomplished, and these halogen derivatives are more active pharmacologically than the hydrocarbon from which they are derived. The bromo and iodo derivatives of methane, ethane and ethylene are more or less rapidly hydrolysed into the corresponding alcohol, or, by the elimination of the halogen acid are converted into the corresponding hydrocarbon. They usually react in this manner so readily that they are of little use in clinical medicine. The chlorine substitution products of these hydrocarbons, on the other hand, are stable, and do not dissociate to any appreciable extent: they act on living cells to produce narcosis as molecular entities, the entire molecule being unchanged.

Hydroxyl Substitution Products: The Alcohols. When a hydroxyl radical (OH) is substituted for an hydrogen atom of a hydrocarbon, an alcohol is formed.

Thus:



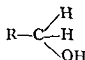
This hydroxyl substitution weakens the narcotic potency of the compound so formed relative to its parent hydrocarbon, and ethyl alcohol is a less potent narcotic than its corresponding hydrocarbon, ethane (C_2H_6). When, moreover, the number of hydroxyl radicals is increased, narcotic potency progressively diminishes with each additional substitution of an hydroxyl radical. In the series shown in Table 2, the narcotic potency diminishes from ethane through ethyl alcohol to glycol, which is a di-hydroxy alcohol, until at length the tri-hydroxylic alcohol, glycerol, is inert as a narcotic.

TABLE 2.

THE RELATION OF HYDROXYL SUBSTITUTION TO NARCOTIC POTENCY.

DRUG	FORMULA	B.P. °C.	STATE	NARCOTIC POTENCY
Ethane	C_2H_6	−85·4	Gas	Greatest
Ethyl alcohol ...	$C_2H_5(OH)$	78·5	Liquid	↓
Glycol	$C_2H_4(OH)_2$	195·0	Liquid	↓
Glycerol	$C_3H_5(OH)_3$	295·0	Liquid	Least

The primary alcohols shown in Table 1 are substitution products of the paraffin series of hydrocarbons. They are primary, saturated, mono-hydroxylic alcohols whose structural formula is seen below.



Primary alcohol
(where R represents an alkyl group)

Primary alcohols are readily oxidised, and this is in marked contrast to the chemical inertness of their corresponding hydrocarbons. The primary alcohols listed in Table 1 are of little use

substitution is carried to the complete exclusion of the hydrogen atoms of the hydrocarbon, narcotic potency decreases slightly, and in the methane series, carbon tetrachloride ($C.Cl_4$) is a less potent narcotic than chloroform ($CH.Cl_3$). This same effect is seen in the chlorine substitution products of ethylene, for tri-chlor-ethylene ($C_2H.Cl_3$) is a more potent narcotic than tetra-chlor-ethylene (C_2Cl_4).

There is good reason to believe, therefore, that the hydrocarbon nucleus, and the chlorine radical, each plays a part in determining the narcotic potency of the chlorinated aliphatic hydrocarbons. At the same time, the chlorine radical is responsible for the deleterious side-actions which these compounds unfortunately possess. They are protoplasmic poisons, and produce degenerative changes in the cells of the liver and the kidneys. The higher members also depress the myocardium, and produce cardiac arrythmias, and during chloroform anæsthesia, ventricular fibrillation may occur. These deleterious side-actions are attributed directly to the presence of the chlorine radicals, and, moreover, they increase in intensity with each additional chlorine radical present in the molecule of the drug. Thus, ethyl chloride (C_2H_5Cl) is less of a protoplasmic poison than chloroform ($CH.Cl_3$).

The dominant pharmacological action of these three homologous series of chlorine substitution products is narcosis, and the narcotic potency of the chlorinated derivatives of a particular hydrocarbon increases with the number of chlorine radicals present, provided that the hydrogen atoms are not completely replaced. An homologous series of chlorine-substituted hydrocarbons, whether derived from the paraffins, the olefins or the acetylenes, obeys the law of homologous series, just as do their parent hydrocarbons. The clinical value of the chloro-hydrocarbons as narcotics, however, is frequently stultified by the deleterious side-actions which the chlorine radical so often introduces.

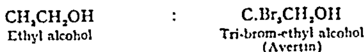
Amino Substitution Products. The alkyl amines are formed by the substitution of an amino group ($-NH_2$) for the hydrogen atom of the hydrocarbon. The introduction of this amino group completely destroys the narcotic action of the hydrocarbon, and alkyl amines are not narcotics

tissues. Their importance in narcosis lies in the substitution and oxidation products which may be obtained so readily from them.

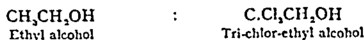
Substitution Products of the Alcohols

Halogen Alcohols. Halogen atoms may be substituted for the hydrogen atoms in the aliphatic chain of a mono-hydroxylic alcohol.

Thus:



CH_3CH_2OH : $C.Br_3CH_2OH$
Ethyl alcohol — Tri-brom-ethyl alcohol (Avertin)



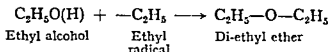
CH_3CH_2OH : $C.Cl_3CH_2OH$
Ethyl alcohol — Tri-chlor-ethyl alcohol

In each instance, the substitution of the halogen radical increases the narcotic potency of the substitution product, and the bromine compound avertin is a more powerful narcotic than the chlorine compound. It is also less of a protoplasmic poison, mainly, it is thought, because it is less stable.

Derivatives of the Alcohols

The Ethers. The ethers are alkyl oxides, and are formed by the substitution of an alkyl group for the hydrogen atom of the hydroxyl group of an alcohol.

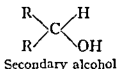
Thus:



$$C_2H_5O(H) + -C_2H_5 \longrightarrow C_2H_5-O-C_2H_5$$
Ethyl alcohol — Ethyl radical — Di-ethyl ether

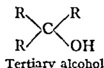
The structural formula of the saturated simple ethers is R - O - R, and for saturated mixed ethers it is R′ - O - R, where R and R′ represent different alkyl groups. By substitution, an homologous series of saturated ethers may be built up whose narcotic potency increases with the length of the carbon chain of the alkyl groups; but a limit is eventually reached when the influence of the physical properties—attendant on the rise of molecular weight, diminution of volatility, etc.—hinders narcotic

as narcotics in clinical medicine, but amongst their oxidation and substitution products are to be found some of the most valuable anæsthetics used in clinical practice.



Secondary alcohol

The **saturated secondary alcohols**, whose structural formula is seen above, are important to this discussion only because they are the source of ketones.



Tertiary alcohol

The **saturated tertiary alcohols**, which have three alkyl groups in their structural formula, are more potent than the primary alcohols. Tertiary amyl alcohol ($C_5H_{11}OH$), amylene hydrate, is the most useful narcotic amongst the tertiary alcohols.

The **unsaturated alcohols** are formed by the substitution of an hydroxyl group for an hydrogen atom of an unsaturated hydrocarbon, and, as with the hydrocarbons, the unsaturated alcohols are more potent narcotics than saturated alcohols.

The only possible hydroxyl substitution product of the first member of the olefin series, ethylene ($CH_2{=}CH_2$), is vinyl alcohol, whose formula is $CH_2{=}CH.OH$, and its name is derived from the vinyl radical ($CH_2{=}CH-$). Vinyl alcohol is a secondary alcohol, and is unsaturated, since it contains a double bond linking the carbon atoms. It is the only unsaturated alcohol relevant to this discussion, for it is the source of di-vinyl ether.

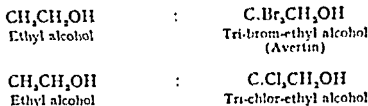
The dominant pharmacological action of the members of the alcohol series is narcosis. They obey the law of homologous series, but are less potent narcotics than their corresponding hydrocarbons This lack of narcotic potency is attributed to the presence of the hydroxyl radical which in addition introduces irritating properties probably due to a dehydrating action on living

tissues. Their importance in narcosis lies in the substitution and oxidation products which may be obtained so readily from them.

Substitution Products of the Alcohols

Halogen Alcohols. Halogen atoms may be substituted for the hydrogen atoms in the aliphatic chain of a mono-hydroxylic alcohol.

Thus:



CH_3CH_2OH (Ethyl alcohol) : $C.Br_3CH_2OH$ (Tri-brom-ethyl alcohol (Avertin))

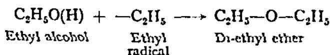
CH_3CH_2OH (Ethyl alcohol) : $C.Cl_3CH_2OH$ (Tri-chlor-ethyl alcohol)

In each instance, the substitution of the halogen radical increases the narcotic potency of the substitution product, and the bromine compound avertin is a more powerful narcotic than the chlorine compound. It is also less of a protoplasmic poison, mainly, it is thought, because it is less stable.

Derivatives of the Alcohols

The Ethers. The ethers are alkyl oxides, and are formed by the substitution of an alkyl group for the hydrogen atom of the hydroxyl group of an alcohol.

Thus:



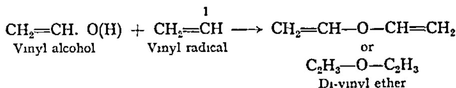
$C_2H_5O(H) + -C_2H_5 \longrightarrow C_2H_5-O-C_2H_5$

Ethyl alcohol + Ethyl radical → Di-ethyl ether

The structural formula of the saturated simple ethers is R - O - R, and for saturated mixed ethers it is R′ - O - R, where R and R′ represent different alkyl groups. By substitution, an homologous series of saturated ethers may be built up whose narcotic potency increases with the length of the carbon chain of the alkyl groups; but a limit is eventually reached when the influence of the physical properties—attendant on the rise of molecular weight, diminution of volatility, etc.—hinders narcotic

action. Simple unsaturated ethers are also formed by the substitution of an unsaturated alkyl group for the hydrogen atom of the hydroxyl group of an unsaturated alcohol.

Thus:

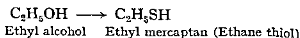


The series of simple saturated ethers are more potent narcotics than the corresponding alcohol series. They obey the law of homologous series, but are irritating to cell protoplasm when used in high concentrations In clinical medicine, di-ethyl ether is the most commonly used simple ether, and the presence of the ethyl radical in the molecule of this narcotic appears to combine narcotic potency with a proper compromise between stability and reactivity.

The cyclic ether, ethylene oxide $\left(CH_2—CH_2 \text{ bridged by } O\right)$ is inert solely because of its instability, and the unsaturated di-vinyl ether, which is sufficiently stable, is neither so potent nor so irritating to cell protoplasm as the simple ethers. Henderson and Haggard (1926) state that the ethers rarely cause organic degeneration of protoplasm, and this would be considered by many to be an understatement.

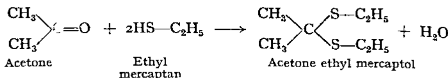
The Sulphur Derivatives. When a sulphur atom replaces the oxygen atom of the hydroxyl group of an alcohol, a *mercaptan*, or *thiol*, is formed.

Thus:



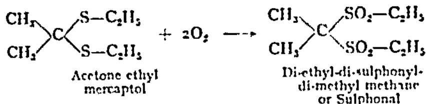
The action of ethyl mercaptan on a ketone produces a *di-thio-ether* or a *mercaptol*

Thus.



And the oxidation of these thio-ethers produces the *di-sulphones*.

Thus:



Sulphonal, trional and tetronal all have slight narcotic powers. These di-sulphones which are not important in clinical anæsthesia, are interesting because they illustrate the relative narcotic effectiveness of the methyl and ethyl groups. Table 3 illustrates this point, and in it the different di-sulphones are labelled alphabetically to facilitate description.

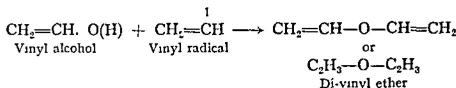
The effect of the substitution of ethyl radicals for methyl radicals in the di-methyl sulphones is seen in Table 3. Compound A, which contains four methyl radicals, is ineffective as a narcotic. Compounds B and C are both narcotics, and Compound C, with two ethyl radicals, is twice as effective narcotically as Compound B, which has only one ethyl radical.

A similar result is obtained in the di-ethyl sulphones when ethyl radicals are substituted for methyl radicals. Compound D (sulphonal), which has two methyl radicals, is a less potent narcotic than Compound E (trional), which has one methyl and three ethyl radicals, and Compound E, in turn, is less potent than Compound F (tetronal), which has four ethyl radicals.

Since Compound D is a more potent narcotic than Compound C, it follows that the effect of this type of substitution on narcotic potency is greater in the sulphones than in the ketones, and illustrates the fact that the ethyl radical confers greater narcotic potency than the methyl radical. Baumann and Kast (1890) asserted that the $SO_2-C_2H_5$ group is essential to the narcotic potency of the di-sulphones.

action. Simple unsaturated ethers are also formed by the substitution of an unsaturated alkyl group for the hydrogen atom of the hydroxyl group of an unsaturated alcohol.

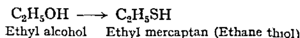
Thus:



The series of simple saturated ethers are more potent narcotics than the corresponding alcohol series. They obey the law of homologous series, but are irritating to cell protoplasm when used in high concentrations In clinical medicine, di-ethyl ether is the most commonly used simple ether, and the presence of the ethyl radical in the molecule of this narcotic appears to combine narcotic potency with a proper compromise between stability and reactivity. The cyclic ether, ethylene oxide ($CH_2{-}O{-}CH_2$) is inert solely because of its instability, and the unsaturated di-vinyl ether, which is sufficiently stable, is neither so potent nor so irritating to cell protoplasm as the simple ethers. Henderson and Haggard (1926) state that the ethers rarely cause organic degeneration of protoplasm, and this would be considered by many to be an understatement.

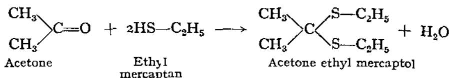
The Sulphur Derivatives. When a sulphur atom replaces the oxygen atom of the hydroxyl group of an alcohol, a *mercaptan*, or *thiol*, is formed

Thus:



The action of ethyl mercaptan on a ketone produces a *di-thio-ether* or a *mercaptol*

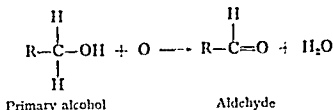
Thus:

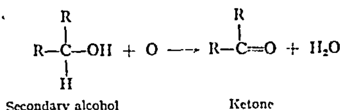


The Oxidation Products of the Alcohols

When primary alcohols are oxidised, aldehydes are produced, while the oxidation of a secondary alcohol results in the production of a ketone.

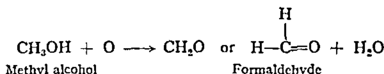
Thus:





The Aldehydes. The aldehydes series of drugs is formed by the oxidation of the primary alcohols, and this results in compounds in which an oxygen atom is united to the carbon atom of the alcohol with the formation of a carbonyl group ($>C=O$).

Thus:



The members of this series are more potent narcotics than their corresponding alcohols, but their anæsthetic action is overshadowed by the intense irritation of the mucous membrane of the respiratory tract which they produce. The lower members are very soluble in water, and, in consequence, the lower aldehydes, such as formaldehyde, produce their irritating action primarily upon the upper respiratory tract On this account, the aldehydes are unsuitable for use in clinical practice.

Aldehydes readily form polymetric compounds, which are condensation products with the same percentage composition but

TABLE 3

THE EFFECT OF THE SUBSTITUTION OF ETHYL RADICALS ON NARCOTIC POTENCY

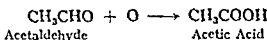
	Di-methyl Ketones		Methyl-ethyl Ketones		Di-ethyl Ketones
Di-methyl Sulphones	$\begin{matrix}CH_3\\CH_3\end{matrix}>C<\begin{matrix}SO_2CH_3\\SO_2CH_3\end{matrix}$ Compound A.	<	$\begin{matrix}C_2H_5\\CH_3\end{matrix}>C<\begin{matrix}SO_2-CH_3\\SO_2-CH_3\end{matrix}$ Compound B.	<	$\begin{matrix}C_2H_5\\C_2H_5\end{matrix}>C<\begin{matrix}SO_2-CH_3\\SO_2-CH_3\end{matrix}$ Compound C.
Di-ethyl Sulphones	$\begin{matrix}CH_3\\CH_3\end{matrix}>C<\begin{matrix}SO_2-C_2H_5\\SO_2-C_2H_5\end{matrix}$ Compound D (Sulphonal)	<	$\begin{matrix}C_2H_5\\CH_3\end{matrix}>C<\begin{matrix}SO_2-C_2H_5\\SO_2-C_2H_5\end{matrix}$ Compound E. (Trional)	<	$\begin{matrix}C_2H_5\\C_2H_5\end{matrix}>C<\begin{matrix}SO_2-C_2H_5\\SO_2-C_2H_5\end{matrix}$ Compound F. (Tetronal)

Chloral is a stable compound with narcotic properties, and it is more potent than its corresponding alcohol. It is the most widely used aldehyde, and is of interest because it was the first narcotic to be prepared synthetically. The aldehyde group $\left({}^{H}\!\!>C{=}O \right)$ makes it a very reactive compound, and of the many chloral derivatives which have been prepared, none possesses advantages over chloral. Chloral is used as an intravenous anæsthetic in veterinary surgery.

Oxidation Products of the Aldehydes

The Organic Acids. The organic acids are the oxidation products of the aldehydes.

Thus:



$$CH_3CHO + O \longrightarrow CH_3COOH$$

Acetaldehyde — Acetic Acid

The introduction of the carboxyl group (CO OH) destroys narcotic potency, and the organic acids are not narcotics.

Derivatives of Organic Acids

The Esters. The esters of fatty acids may be formed by the elimination of water between an alcohol and an organic acid.

Thus:



$$R.CO(OH + H)OR' \longrightarrow R.CO.O.R' + H_2O$$

Fatty acid — Ester

The esters of inorganic oxy-acids, generally speaking, fail to exhibit narcotic properties. In the case of nitrite compounds, for instance, the more powerful nitrite group $(-O-N{=}O)$ pushes into the background the narcotic properties of the hydrocarbon radical, and the dominant pharmacological action of this group of esters is the " nitrite effect."

The Ethereal Salts. " Ethereal salt " is a term formally used for the esters of organic acids.

Thus:

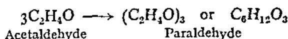


$$CH_3COOH + C_2H_5OH \longrightarrow CH_3COO.C_2H_5 + H_2O$$

Acetic acid — Ethyl acetate

with a molecular weight which is some multiple of that of the parent aldehyde.

Thus:



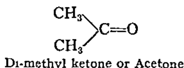
$$3C_2H_4O \longrightarrow (C_2H_4O)_3 \text{ or } C_6H_{12}O_3$$

Acetaldehyde Paraldehyde

In this way acetaldehyde forms a polymetric aldehyde known as *paraldehyde*, which does not possess the intense irritating properties of the aldehyde series of drugs, and is a valuable anæsthetic in clinical practice.

The Ketones. The ketone homologous series of drugs is formed by the oxidation of the secondary alcohols, and this results in compounds in which the bivalent carbonyl group (>C=O) is linked to two alkyl groups

Thus:



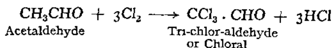
Di-methyl ketone or Acetone

The ketones obey the law of homologous series, and are more powerful narcotics than their corresponding secondary alcohols. Their narcotic potency can be judged by the fact that the vapour of the lowest number of the series, acetone, is slightly more potent than chloroform vapour, for a concentration of acetone, 20,600 parts per million of air, kills mice in ten minutes, and the same result is achieved with 25,900 parts of chloroform per million. Prolonged exposure to acetone does not produce any destructive *action on cell protoplasm. Ketones strongly stimulate the* respiratory centre, but they do not possess the irritating properties of the aldehydes

Substituted Aldehydes

The Halogen Aldehydes. Halogen atoms may be substituted for the hydrogen atoms in the alkyl group of an aldehyde

Thus:



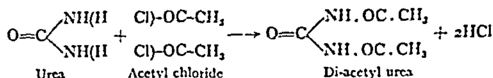
$$CH_3CHO + 3Cl_2 \longrightarrow CCl_3 . CHO + 3HCl$$

Acetaldehyde Tri-chlor-aldehyde or Chloral

SUBSTITUTION PRODUCTS OF UREA

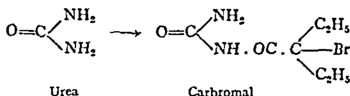
Amino Substituted Urea Derivatives. As an amino compound, urea reacts with acetyl chloride, or with other acyl chlorides, to form acyl compounds analogous to acetamide. These compounds are called ureids, and, like other amides, they are not, in general, narcotics.

Thus:



The substitution of an aliphatic or an aromatic group for the hydrogen atom of urea, however, produces compounds which have weak narcotic properties. Carbromal is an example of such a urea substitution product, but these compounds are not important in clinical anæsthesia.

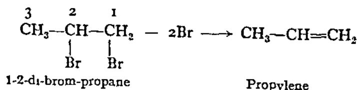
Thus:



2. ALICYCLIC HYDROCARBONS

Cyclopropane. Cyclopropane is an isomer of propylene, the second member of the olefin series of unsaturated hydrocarbons. Propylene has the formula $CH_3-CH=CH_2$, and it may be obtained by heating 1-2 di-brom-propane with sodium.

Thus:

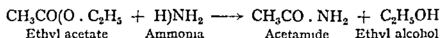


In this reaction, with the loss of two bromine atoms, the adjacent carbon atoms, 1 and 2, become unsaturated and in consequence linked with a double bond.

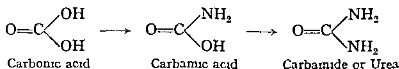
Ethereal salts are very weak narcotics, but it is again interesting to note the narcotic influence of the alkyl group. In the example quoted above it is seen that the substitution of an ethyl radical for the hydrogen atom of the carboxyl group of the inert acetic acid restores narcotic action.

The Amides. When the alkoxy group of an ester is replaced by an amino group (NH_2), an amide is formed, and the narcotic potency of the compound is again destroyed.

Thus:



Urea. *One amide—urea—is, however, important to this discussion* Urea is the di-amide of carbonic acid, and is also called carbamide. Like the simple amides, urea is quite inert as a narcotic, but some of its derivatives are amongst the most important narcotic drugs in clinical medicine. Its formation from carbonic acid, through carbamic acid, is shown below. Carbamic acid has never been isolated, but its salts and esters are known.

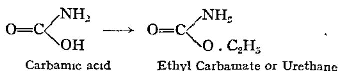


Carbonic acid Carbamic acid Carbamide or Urea

CARBAMIC ACID DERIVATIVES

Carbamates or Urethanes. Carbamic acid forms esters with the various aliphatic alcohols The ethyl ester is called ethyl carbamate or urethane.

Thus:



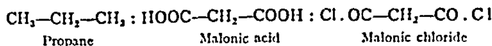
Carbamic acid Ethyl Carbamate or Urethane

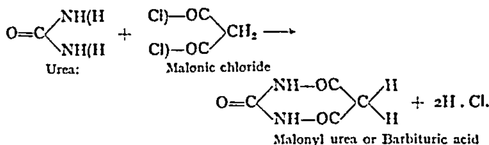
An homologous series of urethanes can be built up which obey the law of homologous series, but they are relatively weak narcotics.

the parent compound of one of the most valuable, and, at the same time, one of the most numerous groups of narcotic drugs used in clinical medicine.

Barbituric acid is formed when urea reacts with the chloride of the di-basic acid, malonic acid; the relationship of malonic acid to propane is shown below.

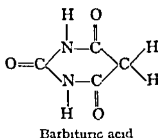
Thus:



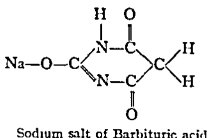


Although barbituric acid does not contain the carboxyl group (COOH) of a true organic acid, it reacts to form salts.

Thus:



Barbituric acid



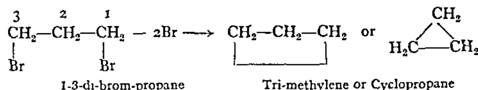
Sodium salt of Barbituric acid

The solubility of the salts of barbituric acid in water is in marked contrast to the relative insolubility of barbituric acid itself and, in consequence, the salts (particularly the sodium salts of barbituric acid) are suitable for use in clinical medicine.

When the two hydrogen atoms of the malonyl end of barbituric acid or its salts are replaced by alkyl groups, a substituted barbituric acid derivative is formed. When the substituents are ethyl

If 1-3-di-brom-propane, an isomer of the 1-2 compound, is similarly treated, the terminal carbon atoms, 1 and 3, become linked together with a single bond and a three membered carbon ring compound, cyclopropane, is formed

Thus:



In this manner, an open-chain compound is converted into a closed or cyclic compound. Cyclopropane is, therefore, a carbocyclic compound and, since there are no double bonds between the carbon atoms, is it saturated. It is termed an ali-cyclic hydrocarbon to suggest a similarity to the aliphatic group and to distinguish this type of compound from the carbo-cyclic hydrocarbons related to benzene.

An homologous series of saturated ali-cyclic hydrocarbons, isomers of the olefin series, may be built up, and this series obeys the law of homologous series. The first member, *cyclopropane*, is the only member to be employed in clinical anæsthesia. It is a potent narcotic, whose action is similar to that of the olefin series. It is not a protoplasmic poison, and, according to Bourne (1934), does not cause liver degeneration. It does produce bradycardia and cardiac arrythmias in man, and it may produce ventricular fibrillation in man at high concentrations.

3. HETEROCYCLIC COMPOUNDS

(a) Cyclic Ureids

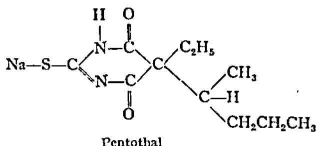
It has been seen (page 31) that the reaction of urea with the acyl chlorides of mono-basic acids produces acyl compounds called ureids, which are open-chain compounds and, like other aliphatic amides, are usually not narcotic.

When, however, the acyl chlorides of a di-basic acid react with urea, a cyclic compound is formed. One cyclic ureid, barbituric acid, is of the greatest importance in this discussion, for it forms

The presence of the alkyl radicals or groups substituted for the two hydrogen atoms of the malonyl residue plays a dominant rôle in determining the narcotic potency of the barbiturates. The influence of this type of alkyl substitution has already been observed in aliphatic hydrocarbons and their derivatives, such as the urethanes. Generally speaking, the narcotic potency of the barbiturates increases as the length of the carbon chain of these substituted alkyl groups, and, according to Sholne (1932), reaches its greatest potency with the amyl group. An enormous number of different barbiturates may be built up by variations in the molecular constitution of the substituted alkyl side-chain, and they vary greatly in the intensity of their narcotic action. A. J. Clark (1937) stated that the number of possible barbiturate homologues, none containing more than six carbon atoms in a side-chain, is 1,225.

Just as urea gives rise to the barbiturates, so does the sulphur analogue of urea, thio-urea, give rise to the thio-barbiturates. This important variation in barbiturate synthesis leads, for example, to *pentothal* which, to date, is the most potent rapidly acting barbiturate in common clinical use.

Thus:



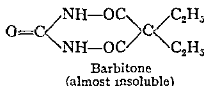
Pentothal

(b) The Alkaloids and Allied Substances

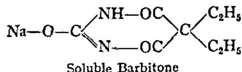
This group of narcotics consists of alkaloids extracted from plants and synthetic substances, which, by reason of their chemical constitution and behaviour, are allied to the narcotic alkaloids. Orderly classification is difficult, and these narcotics consist of aromatic carbocyclic hydrocarbons and heterocyclic nitrogenous bases related to pyridine, quinoline, isoquinoline and pyrrole. They are stable compounds, and form salts soluble in water.

groups, barbitone, which is almost insoluble, is formed from barbituric acid, and soluble barbitone is formed from the sodium salt of barbituric acid

Thus:



Barbitone
(almost insoluble)

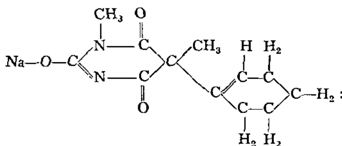


Soluble Barbitone

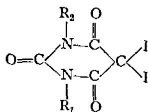
The Barbiturates. In anæsthesia, barbituric acid, its salts and its derivatives, are known generically as barbiturates. They are heterocyclic compounds, since the atoms which comprise the barbiturate ring are not all of the same kind; the narcotic potency of the barbiturates must be attributed, in part, to the fact that they are close-ring compounds, for the potency of these cyclic amides is in marked contrast to the impotency of the corresponding acyclic amides of urea, such as di-acetyl urea (see page 31).

The narcotic potency of the barbiturates has been attributed to the presence of the group $-\overset{\overset{H}{|}}{N}-\overset{\overset{O}{\|}}{C}-$ in the molecular constitution of these drugs, but it is doubtful whether this group, per se, which is called the *Nebelthau factor*, exercises the dominant *narcotic influence, which, in the past, has been attributed to it.* It is present in the aliphatic ureids, and while a few of these acyclic compounds, such as carbromal, are weak narcotics, the majority are inert. *Evipan*, on the other hand, contains four such groups in its molecule it seems that the hetero-cyclic barbiturate ring, rather than the presence of this specific group, is the important factor.

Thus:



Evipan

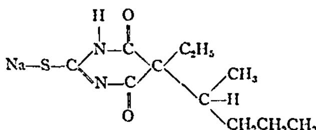


Barbiturate Ring

The presence of the alkyl radicals or groups substituted for the two hydrogen atoms of the malonyl residue plays a dominant rôle in determining the narcotic potency of the barbiturates. The influence of this type of alkyl substitution has already been observed in aliphatic hydrocarbons and their derivatives, such as the urethanes. Generally speaking, the narcotic potency of the barbiturates increases as the length of the carbon chain of these substituted alkyl groups, and, according to Sholne (1932), reaches its greatest potency with the amyl group. An enormous number of different barbiturates may be built up by variations in the molecular constitution of the substituted alkyl side-chain, and they vary greatly in the intensity of their narcotic action. A. J. Clark (1937) stated that the number of possible barbiturate homologues, none containing more than six carbon atoms in a side-chain, is 1,225.

Just as urea gives rise to the barbiturates, so does the sulphur analogue of urea, thio-urea, give rise to the thio-barbiturates. This important variation in barbiturate synthesis leads, for example, to *pentothal* which, to date, is the most potent rapidly acting barbiturate in common clinical use.

Thus:



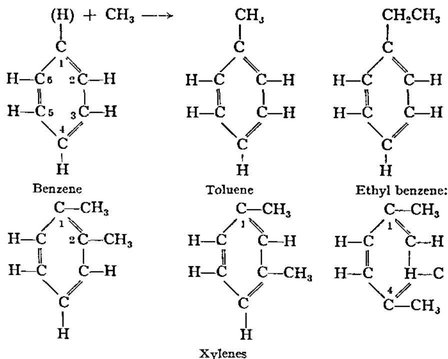
Pentothal

(b) The Alkaloids and Allied Substances

This group of narcotics consists of alkaloids extracted from plants and synthetic substances, which, by reason of their chemical constitution and behaviour, are allied to the narcotic alkaloids. Orderly classification is difficult, and these narcotics consist of aromatic carbocyclic hydrocarbons and heterocyclic nitrogenous bases related to pyridine, quinoline, isoquinoline and pyrrole. They are stable compounds, and form salts soluble in water.

Aromatic Compounds. *Benzene* stands in the same relation to aromatic carbo-cyclic hydrocarbons as does methane to aliphatic hydrocarbons. As indicated by the structural formula, the benzene molecule consists of a plane hexagonal ring of six CH groups. Although the presence of the double bonds might suggest unsaturation of the same type as shown by the olefines, the conjugation (alternate single-double links) around the ring in fact confers an almost saturated behaviour on benzene and its homologues, and is the basis of its aromatic character.

By the substitution of a methyl group for an hydrogen atom of benzene, toluene (C_7H_8) is formed, and by the substitution of larger alkyl groups, an homologous series of alkyl benzenes may be built up. More than one hydrogen atom of the parent benzene may be replaced, leading to di-substituted products such as xylenes



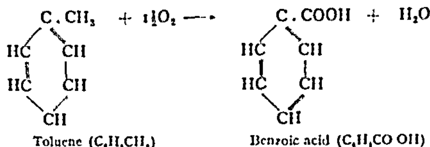
Benzene Toluene Ethyl benzene:

Xylenes

Just as in the paraffin series, so also in the alkyl-benzene series, halogen, hydroxyl, carboxyl, amino, etc. substitution products may be formed, and the substituents may be introduced either into the side-chain or into the ring itself. Thus, when toluene is

oxidised the methyl group is converted into a carboxyl group, and mono-carboxy-benzene (benzoic acid) is formed.

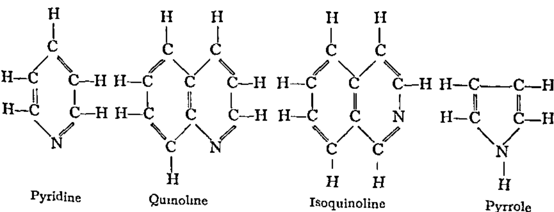
Thus:



Toluene ($C_6H_5CH_3$) Benzoic acid ($C_6H_5CO\,OH$)

A characteristic of these substitution products is that both parts of the compound, the benzene nucleus on the one hand, and the aliphatic side-chain on the other, retain their individual properties. This same characteristic has been seen to apply in the barbiturate compounds.

Heterocyclic Compounds. Pyridine is a heterocyclic nitrogenous base which shows " aromatic character " similar to benzene. Its formula shows it to be a hexagonal ring, in which one of the CH groups of benzene has been replaced by a nitrogen atom. Quinoline consists of a benzene ring fused with a pyridine ring, and linked so that the nitrogen atom is next to the benzene ring. Isoquinoline also consists of a benzene ring fused with a pyridine ring, but in this case the two rings are linked, so that the nitrogen

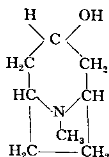


Pyridine Quinoline Isoquinoline Pyrrole

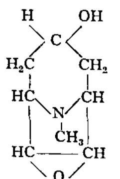
atom is separated from the benzene ring by one CH group. Pyrrole is a five membered heterocyclic ring containing an imino group (= NH—).

Narcotic Alkaloids and Allied Substances. COCAINE was the first narcotic alkaloid to be used in clinical practice as a local anæsthetic (1884), and it proved to be related to two alkaloids of the solanaceous group, *atropine* and *scopolamine*.

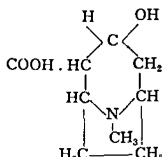
The nitrogenous base of ATROPINE is tropine, which is a seven membered cyclic secondary alcohol (cyclo-eptanol), symmetrically bridged by a methyl-imino group ($>N.CH_3$). It is seen to be a bi-heterocyclic compound containing a reduced pyrrole, i.e., a pyrrollidine ring, fused to a reduced pyridine, i.e., a piperidine ring, so that three members are common to both rings.



Tropine



(Epoxy Group)
Scopine:



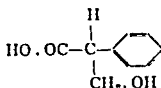
Ecgonine

Scopine, the nitrogenous base of SCOPOLAMINE, differs from tropine only in the presence of an ethylene oxide, an epoxy group.

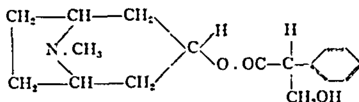
Both tropine and scopine, functioning as alcohols, form esters with carboxylic acids, and the esters which they form with tropic acid are respectively atropine and scopolamine. Atropine is optically inactive. It paralyses para-sympathetics, and is not a

narcotic. Scopolamine is lævo-rotatory; it paralyses the parasympathetics, and is a potent narcotic.

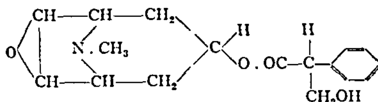
Thus:



Tropic Acid



Atropine ($C_{17}H_{23}O_3N$) Molecular weight, 289 6



Scopolamine ($C_{17}H_{21}O_4N$) : Molecular weight, 303 2.

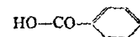
Ecgonine, the nitrogenous base of COCAINE, is a seven membered bi-cyclic compound containing a pyrrollidine ring fused to a piperidine ring, and bridged by a methyl-imino group. It differs from tropine only by the presence of a carboxyl group, and it is tropine carboxylic acid. Ecgonine is both an alcohol and a carboxyl acid, and the hydroxyl and carboxyl groups are beta to one another, for they are linked to adjacent carbon atoms.

If the carboxyl group of ecgonine is esterified with methyl alcohol, and the hydroxyl group benzoated, i.e., made to form an ester with benzoic acid, cocaine is produced. Cocaine is a potent narcotic, but is very toxic.

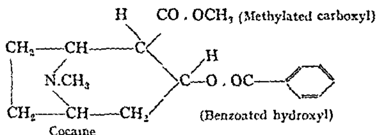
With the introduction of cocaine, the importance of local anæsthesia was quickly recognized, and led to a search for compounds possessing the narcotic properties and potency of cocaine

but lacking its highly deleterious side-actions. An isomer of cocaine, ALPHA COCAINE, was soon isolated, and although this compound is similar to cocaine in its structure and properties, it proved to be inert as a narcotic. In alpha cocaine, however, the carboxyl and hydroxyl groups are both linked to the same carbon atom, and are alpha to one another—a form of linkage which is known as the *alpha hydroxyl relation.*

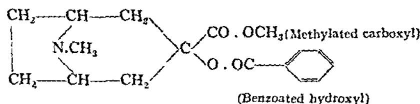
Thus:



Benzoic acid:



Cocaine

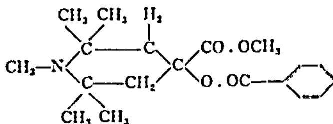


Alpha Cocaine (showing Alpha hydroxyl relation)

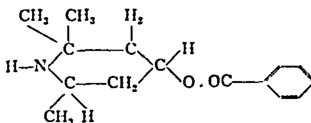
ALPHA EUCAINE was then synthetised. It represents a simplification of the nitrogen containing ring system. Alpha and BETA EUCAINE are both benzoates of substituted hydroxy piperidine ring. Alpha eucaine shows a strong structural resemblance to alpha cocaine, and both contain the alpha hydroxyl relationship. It has, however, narcotic properties, and is less toxic than cocaine, but it produces local irritation at the site of injection BETA EUCAINE differs from the alpha compound for two reasons; firstly, in the absence of the methlyated carboxyl group, and, secondly, in that the ring system contains fewer methyl groups. It is less toxic

than cocaine or alpha eucaine, and is a narcotic comparable in potency to cocaine.

Thus:



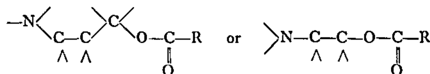
Alpha Eucaine:



Beta Eucaine:

This study of cocaine and eucaine suggested that compounds containing *alcohol-amine-ester grouping* might prove to have narcotic properties. The alcohol-amine-ester grouping is shown below, and reference to the structural formulæ of cocaine and eucaine will show its relationship to those compounds.

Thus:



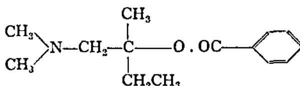
Alcohol-amine-ester or Alkamine ester grouping

The supposition proved correct; and it was found, moreover, that the nitrogen atom and the oxygen atom of the hydroxyl group need not be separated by three carbon atoms; two carbon atoms were sufficient. Compounds with a three carbon alkamine ester chain are benzoic acid esters of amino alcohols, and those with a two-carbon chain are ethanol amine esters.

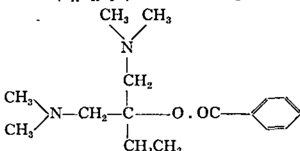
This discovery led to the synthesis of two ethanol amine esters, STOVAINE and ALYPINE. The narcotic potency of these drugs is

similar to that of cocaine. They are rapid in their action, but they do not possess the deleterious side-actions of cocaine.

Thus:

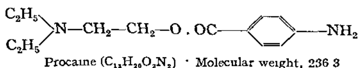


Stovaine ($C_{14}H_{21}O_2N$) : Molecular weight, 235·3

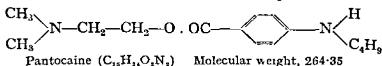


Alypine ($C_{16}H_{26}O_2N_2$) : Molecular weight, 278 3

The next synthetic narcotic, NOVOCAINE—or PROCAINE, as it is usually termed nowadays—has proved to be one of the most universally used and valued local anæsthetics. Its structural formula shows the presence of the two-carbon alkamine ester chain, but an amino group has been introduced into the benzene ring. Procaine is a potent local anæsthetic, and it is not a toxic drug. PANTOCAINE, whose structural formula is similar to that of procaine, is a more potent, and at the same time a more toxic, drug than procaine The length of the aliphatic side-chain substituted for the hydrogen atom of the substituted amino group of benzene is probably responsible for its increased potency relative to procaine, while its two methyl groups are the probable reason for its toxicity.

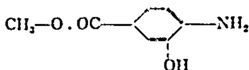


Procaine ($C_{13}H_{20}O_2N_2$) · Molecular weight, 236 3

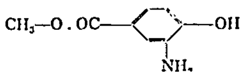


Pantocaine ($C_{15}H_{24}O_2N_2$) Molecular weight, 264·35

The next step in synthesis was the omission of the alkanolamine group, and this results in the formation of simple alkyl esters of amino benzoic acid, such as ORTHOFORM and NEW ORTHOFORM. These compounds are amino phenolic benzoic esters, and they are not suitable for use as infiltration anæsthetics because of their relative insolubility and instability. They are employed in clinical medicine as surface anæsthetics.



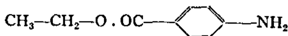
Orthoform: (Methyl ester of para-amino-hydroxy-benzoic acid)



New Orthoform: (Methyl ester of met-amino-para-hydroxy-benzoic acid)

Finally, the omission of the phenolic group of amino phenolic benzoic esters results in compounds such as ANESTHESINE, which differs from procaine only in the absence of the terminal di-ethyl amino group. Anesthesine is employed as a surface anæsthetic because of its relative insolubility and instability.

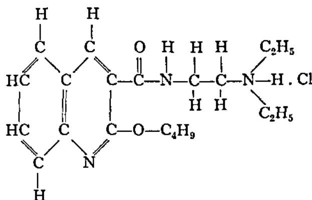
Thus:



Anesthesine (Ethyl ester of para-amino-benzoic acid)

The only narcotic quinoline derivative in common clinical use is NUPERCAINE. Its structural formula is seen below. The aliphatic side-chain attached to the beta carbon atom of the pyridine ring of this quinoline nucleus is not an alkamine ester, but an amino-amide group. Nupercaine is one of the most potent narcotics

employed in clinical practice, and is non-toxic when used in therapeutic doses.



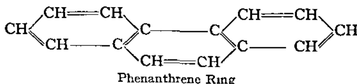
Nupercaine hydrochloride ($C_{20}H_{29}O_2N_3H.Cl$)
Molecular weight, 379·46

Opium contains a variable amount of a large number of alkaloids, which belong to two groups.

Papaverine, narcotine, laudanosine etc., are derived not from quinoline but from isoquinoline. These isoquinoline derivatives vary considerably in the action, for papaverine and narcotine are mild narcotics, but laudanosine is a powerful convulsant.

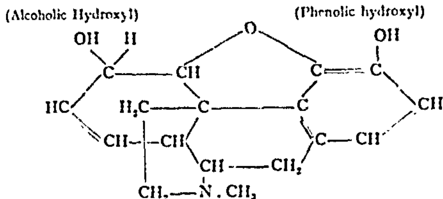
Morphine, codeine and heroin, on the other hand, are derivatives of phenanthrene, and they are amongst the most valuable narcotics used in medicine.

Thus:



Phenanthrene Ring

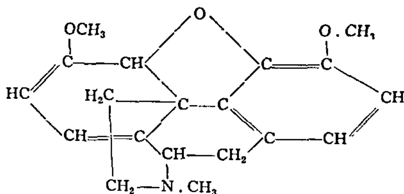
The structural formula of morphine, given below, is the generally accepted formula of Robinson. It is seen that morphine contains an alcoholic hydroxyl group, which is responsible for the convulsant effect; a phenolic hydroxyl group, which is responsible for the narcotic effect; and an ethereal oxygen and a tertiary nitrogen, which give the compound its basic properties including its ability to form salts



Morphine ($C_{17}H_{19}NO_3$) : Molecular weight, 285·3

The substitution of alkyl groups for the hydrogen atom of the hydroxyl groups of morphine produces alterations in the narcotic potency of the compound. Thus, when the hydrogen atom of the phenolic hydroxyl is replaced by a methyl group, *codeine* is formed, and narcotic potency is diminished. When both hydroxyl groups are acetylated ($-OH \rightarrow -O-\overset{\overset{\textstyle O}{\|}}{C}-CH_3$), *heroin* is formed, and narcotic potency is greatly increased; but when both hydroxyl groups are methylated, *thebaine* is produced, and this drug is so convulsant that it is often classified with convulsant drugs such as strychnine. The structural formula of thebaine shows that modifications in the linkage of the carbon atoms also occurs.

Thus:


Thebaine ($C_{19}H_{21}NO_3$) : Molecular weight, 311·36

These examples serve to demonstrate the influence of particular chemical radicals, or groups, and the empiric relation that exists

between narcotic action and the molecular constitution of narcotic drugs, may be summarised briefly as follows:

Narcotics having similar molecular constitutions, as a rule, possess a similar narcotic action. The narcotic potency of the members of a homologous series of aliphatic hydrocarbons increases with the length of the carbon chain, and, within limits, unsaturated compounds are more potent than the corresponding saturated hydrocarbons. In like manner, narcotic potency in the barbiturates and in the aromatic heterocyclic compounds increases with the length of the aliphatic side-chain attached to the parent nucleus. While the introduction of alkyl groups increases the length of the carbon chain or causes branching, there is reason to believe, in addition, that the ethyl group is more effective than the methyl group, which also appears to introduce toxic properties. The substitution of hydroxyl groups (OH) decreases narcotic action, but this is restored again when alcohols are oxidised to aldehydes and ketones. The alkyl oxides, the ethers, are potent narcotics. The substitution of chlorine atoms for the hydrogen atoms of the parent hydrocarbon, their alcohols, and the oxidation products of these alcohols, in each case increases narcotic potency, but invariably introduces harmful side-action. Amino (NH_2), carboxyl (CO OH) and nitrite ($-O-N=O$) radicals, substituted or added, destroy narcotic action, but the substitution of alkyl groups for the hydrogen atom of the carboxyl or amino groups restores narcotic potency in a measure.

Cyclic compounds, generally speaking, are more potent narcotics than open-chain compounds. For example, most aliphatic ureids are inert, but the barbiturates, which are heterocyclic ureids, are potent and valuable narcotics. The heterocyclic narcotics illustrate the influence on narcotic action of the nucleus, on the one hand, and, on the other, that of the side-chain. In these compounds, the presence of the alkamine ester grouping appears to confer narcotic potency, as shown by the number of synthetic compounds of this type in common clinical use, while the alpha hydroxyl relation probably detracts from the narcotic potency of a compound.

This empiric relation between the biological response of living cells to narcotics, and the molecular constitution of narcotic drugs,

is clearly more than a casual one. It is concerned with the ability of the narcotic to combine with specific entities of cell protoplasm, and, once fixed, to modify the functional activity of the cell in a fashion that has been defined as narcosis. The influence of specific chemical radicals and groups may be illustrated by comparing, in a heterogeneous cell system such as man, the pharmacological action of three alkaloids with a similar molecular constitution, viz., morphine, codeine and the closely related thebaine.

Morphine combines with the protoplasm of the cells of the central nervous system through its phenolic hydroxyl group, and produces narcosis. When the phenolic hydroxyl is methylated, codeine is formed and this compound combines with cell protoplasm through its alcoholic hydroxyl group. It is a mild convulsant, and is a less powerful narcotic than morphine. From this change of pharmacological action with change in the fixation mechanism, it can be inferred either that codeine is fixed to the same receptor as morphine, but in a different manner, or that it is fixed to different receptors. When both the phenolic and the alcoholic hydroxyl groups of morphine are blocked by methylation, as in thebaine, fixation is effected through a new combined group to different receptors in different types of cells. Thus narcotic action is lost, and the convulsant action becomes the dominant action of the compound.

It appears that the molecular constitution of a substance determines the site of its drug fixation, and the influence of certain radicals and groups in the constitution of narcotics suggests that narcotic fixation and, in turn, the biological response of living cells and enzymes to narcotics, is determined by the specificity of certain narcotic radicals for specific receptors of certain cells, rather than substance specificity.

REFERENCES.

1. Baumann, E, and Kast, A (1890) *Hoppe-Seyl. L.* 14, 52.
2. Clarke, A. J. (1910) "Applied Pharmacology," 7th Ed, p. 230. J. & A Churchill Ltd, London
3. Shonle, H. A (1932). *Anest. & Anelg.*, 2, 210.

CHAPTER III

THE PHYSICAL PROPERTIES OF NARCOTICS AND THEIR RELATION TO PHARMACOLOGICAL ACTION

THE physical properties of narcotic drugs exercise a decided influence on their pharmacological action. Henderson and Haggard (1926) state: "It is often difficult to tell whether in the physiological action [of a drug] the determining factor is physical or chemical, for the two generally run in parallel."

The observations of Hiller (1927) and Marsland (1934) indicate that narcotics act in or on the cell surface, and do not act in the interior of living cells. The sequence of events occurring when a narcotic in an effective concentration is brought into contact with a living cell is as follows:

(1) Uptake of the narcotic by the cell from the extracellular fluid with which it is in contact.
(2) Fixation of the narcotic by the cell.
(3) The biological response of the cell to the mass of narcotic fixed.

From the thesis that fixation and biological response result from the interaction of specific chemical radicals, it follows that the influence which the physical properties of a narcotic undoubtedly exercise upon the biological response is to be found in the extent to which these physical properties help, or hinder, the uptake of the narcotic by the cell, and in this fashion help, or hinder, drug fixation.

Water Solubility. Richet (1893) found that the intensity of narcotic action varied inversely as the solubility of the narcotic in water. Fuhner (1921) showed in the homologous paraffin series (*pentane*, *hexane*, *heptane*, *octane*) that there was a far-reaching parallelism between water solubility and the concentration of narcotic required to paralyse the action of a frogs' heart, and that water solubility decreased as narcotic potency increased

On the basis of these observations, it might be concluded that the narcotic potency of a drug depends upon its inability to dissolve in water but (as Winterstein has pointed out) it is an obvious absurdity to suggest that narcotic potency depends upon such a purely negative property as insolubility in water. Water is the almost universal biological solvent, for tissue fluids contain 90-99% of water, and tissue cells (excluding such specialised cells as adipose tissue, yellow bone marrow, etc.) contain 75-85% of water.

Because of the high water content of living tissue cells, water solubility undoubtedly plays a part in the uptake of narcotics by living cells from the extracellular fluid in which they are immersed or bathed, and this applies alike to a homogeneous population of unicellular organisms and to the cells of a heterogeneous cell system.

When anæsthetics (in contradistinction to narcotics) are discussed, water solubility is a factor of even greater importance; whether blood-borne or local anæsthetics are considered, a certain solubility in water is imperative if an anæsthetic is to be concentrated at the site of its drug fixation in or on the surface of the cells of a heterogeneous cell system. For instance, blood-borne anæsthetics, as the term implies, must be carried in circulating blood which contains 79% of water, to be dissolved in extracellular fluid which contains 90-99% of water, while a local anæsthetic is injected in aqueous solution with syringe and needle to dissolve in extracellular fluid.

The method of approach of all anæsthetic drugs to the site of their drug fixation in or on the surface of tissue cells, therefore, necessitates a certain solubility in water if they are to be effectively concentrated at the site. This certain solubility is conditioned by the potency of the particular narcotic, for there is a minimum threshold concentration for each narcotic, below which it fails to produce a biological response on a given type of living cell.

It may be concluded that in narcosis water solubility plays a part, and in anæsthesia an essential part, in the uptake of the narcotic by living cells.

Table 1 shows the first ten members of the homologous paraffin series, and serves to illustrate how the physical characteristics of

the members of the series change progressively as the carbon chain of the molecular constitution of each successive member increases in length Thus, in each successive member from methane to decane, the water solubility decreases; the boiling point progressively rises; and the volatility, in turn, progressively diminishes. There must then come a time in the series when the water solubility and the maximum vapour pressure at room temperature are too small to allow the drug to be carried in circulating blood and concentrated in extracellular fluid in an effective concentration. When this stage in the series occurs, the drug may be an efficient and a potent narcotic but is ineffective as an anæsthetic. Decane, the tenth member of the paraffin series, is such a drug. It is a potent narcotic, with a boiling point of 168°C. and is very insoluble in water. Its low solubility in water, and the low vapour pressure it exerts at room temperature, prevent its concentration in the extracellular fluid of a heterogeneous cell system in an effective concentration, so that this drug, while a potent narcotic, is inert as an anæsthetic.

Fat Solubility. As the carbon chain of the molecular constitution of each successive member of the paraffin series increases in length, its water solubility decreases while its fat solubility increases

In respect to the carriage of a narcotic drug in circulating blood which contains 2 59% of lipoid, and its solution in extracellular fluid whose lipoid content is 0 7% (circa), a high fat solubility has relatively little influence in determining the absolute solubility of the narcotic in whole blood or extracellular fluid. A very high solubility in fat, such as is found in cyclopropane and chloroform may, however, compensate for the very low water solubility of these drugs, and so increase their absolute solubility in whole blood to a value which permits them to be carried in circulating blood, and to be concentrated in extracellular fluid in an effective solution.

On the other hand, if specialised cells—adipose tissue, yellow bone marrow, etc —are excluded, the fact that tissue cells contain 2·18% of lipoid (most of which is concentrated in the cell membrane) indicates that a high fat solubility will exert a decided influence upon the ability of a narcotic to concentrate in an

effective solution at the site of drug fixation in or on the cell membrane. In this fashion, a high fat solubility will materially help in the uptake of a narcotic drug from extracellular fluid, and, it is inferred, subsequent fixation in or on the cell surface.

The importance of the fat solubility of narcotic drugs was recognised by L. R. Hermann in 1866, and later, H. H. Meyer (1899) and E. Overton (1901), quite independently of one another, observed in an homologous series of narcotics that the intensity of narcotic action increased with the fat solubility of each successive member of the series. But, when narcotics with dissimilar chemical constitutions were compared, the parallel between the intensity of narcotic action and the fat solubility of the narcotic did not apply with the same exactness that had been shown to exist in the narcotics of a homologous series. These observers used olive oil as a standard to estimate the fat solubility of various narcotics, and they expressed their results as the oil/water partition coefficient which is the ratio $\frac{\text{solubility in fat.}}{\text{solubility in water.}}$ Objection has been raised to their results on the ground that the solubility of a narcotic in cell lipoids such as cholesterol and the phosphatides, lecethin, kephalin, cerebrin, cerebrosides etc., differs from its solubility in the chosen standard, olive oil, but such a difference would affect the degree rather than the direction of the relationship.

Meyer and Overton's work resulted in the " LIPOID SOLUBILITY THEORY OF NARCOSIS," and Meyer postulated that " all chemically indifferent *substances, which are soluble in fats or fatty substances,* must exert a narcotic action on living protoplasm, in as far as they can become distributed in it."

This generalization does not bear criticism, for there are drugs —such as many of the benzol derivatives—which have a high oil/water partition coefficient, but do not produce narcosis. Again, morphia and other basic and saline narcotics—which are to all intents and purposes insoluble in fats—produce a state of narcosis in living cells. Aliphatic and other narcotics soluble in fats produce the characteristic narcotic response, not only on cells which contain lipoid but also on enzymes which do not contain lipoid.

It is thus clear that lipoid solubility, though a desirable property, is not an indispensable requisite for narcosis. Narcosis depends upon specific chemical radicals in the molecular constitution of the narcotic which permit the fixation of the drug by the cell or enzyme, and, after fixation has been accomplished, produce the characteristic biological response of narcosis.

The problem is clearer if one assumes that the physical property of solubility influences the biological response of cells to narcotic drugs only in as far as the solubility of the narcotic affects the uptake of the drug by the cell. In this instance, the uptake of the benzol derivatives by tissue cells is rapid and facile, because they are highly soluble in fat; but once they have been concentrated in or on the cell surface, fixation and/or narcotic response by the cell is lacking because narcotic radicals are absent from the molecule of the drug.

Morphia and the basic and saline narcotics obviously possess the necessary narcotic radicals, for they produce narcosis. Fat solubility is not a dominant factor in the mechanism of their uptake by living cells, but they are soluble in water, and water solubility and/or adsorption can readily be responsible for their concentration in an effective solution at the site of drug fixation in cells and enzymes. The uptake of aliphatic narcotics by lipoid free enzymes, in like manner, can be attributed to water solubility and/or adsorption and water solubility plays a dominant role in the uptake of narcotics such as chloral hydrate, alcohol and acetone, whose oil/water partition coefficient is less than unity.

It can be concluded that in a heterogeneous cell system water solubility exerts a dominant influence, and fat solubility exerts at best a minor influence upon the carriage to, and the concentration of, narcotic drugs in extracellular fluid. On the other hand, the uptake of a narcotic from extracellular fluid by any cell system —whether it be a heterogeneous cell population or a population of homogeneous unicellular organisms—is influenced not only by the water solubility, but. also, by the fat solubility of the drug, for tissue cells contain 75-85% of water, and 2-18% of lipoid. When a narcotic possesses the property of fat solubility, this quality will exert a dominant influence upon the uptake of the narcotic by the

cell, for most of the cell lipoid is concentrated in the cell surface, which is the site of drug fixation of narcotics.

Solubility. The physical property of solubility, therefore, exercises a profound influence upon the uptake of narcotic drugs by living tissue cells, and the whole history of chemistry bears witness to the extraordinary importance of solubility.

The solubility of one substance in another depends fundamentally upon the ease with which the two molecules mix. Like molecules mix easily, un-like molecules mix with difficulty. When two kinds of molecules show a hostility to mixing, not only will saturation be accomplished at a lower concentration, but, in an unsaturated solution, the tendency to mutual segregation will give rise to a partial separation or adsorption of one type of molecule at the surface, with consequent lowering of surface tension. The same molecular forces which determine the composition of a saturated solution—whether the solute is a solid, a liquid, or a gas or vapour at a given pressure—operate also in unsaturated solutions, and these molecular forces influence all the factors connected with the "escape tendency" of molecules from the solution.

The escape tendency of molecules may show itself in a number of ways. The precipitation of a solute from a solvent, or its surface adsorption, are manifestations of this force. The escape tendency of molecules may take the form of vapour pressure and, if it is measured by the escape of molecules from one solvent into a second solvent immiscible with the first, this index is a partition coefficient. The escape of one component through a semi-permeable membrane is known as osmosis.

Solubility, surface tension, adsorption, etc., are thus manifestations of the same molecular force, which in each instance has as its object the establishment of a state of equilibrium, and this same force determines the mass of a given narcotic which must escape from extracellular fluid to a particular type of tissue cell to establish a state of equilibrium, in respect of the narcotic within the drug-cell system.

Hence, the uptake of a narcotic drug by living cells from extracellular fluid is essentially the assumption of equilibrium, in respect to the narcotic, within the drug-cell system, and the

fundamental problem of narcotic uptake is to determine to what extent the escape tendency of molecules of the narcotic (from extracellular fluid to the tissue cells themselves) may be expected to vary with the physical nature of the dissolved narcotic, for narcotics range from gases and vapours to liquids and solids.

Narcotic Gases. A gas has been described as an elastic fluid at a temperature above its critical temperature. An ideal gas is completely compressible, and moves by diffusion from a region

THE RELATION OF THE VAPOUR PRESSURE OF DI-ETHYL ETHER TO THE TEMPERATURE.

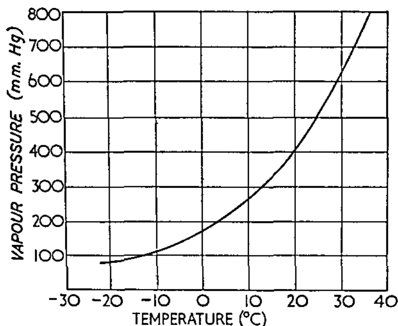


FIGURE 4

of higher pressure to a region of lower pressure, until gaseous equilibrium has been achieved, at a rate directly proportional to its diffusion gradient and inversely proportional to the square root of its density. In the conditions which obtain in clinical anæsthesia, narcotic gases obey the gas laws, and their behaviour can be anticipated according to the formula $pv = RT$.

Narcotic Vapours. A vapour has been described as an elastic fluid below its critical temperature, but not in the liquid state.

The vapour pressure of a liquid increases with the rise of temperature of the liquid. At its boiling point, the vapour pressure of a liquid is equal to that of the atmosphere to which it is exposed; at mean sea level a liquid at its boiling point therefore exerts a vapour pressure of 760 mm. of mercury. If sufficient liquid is present, its vapour pressure at any given temperature is the maximum possible pressure which it can exert at that temperature, and the vapour space is, therefore, saturated. The vapour pressure of a liquid, in equilibrium with its liquid, increases however with rise of temperature more rapidly than does the pressure of a true gas. The deviation of ether vapour from ideal behaviour is illustrated in Figure 4.

Saturated vapours are not compressible; because a vapour is below its critical temperature it will condense (*i.e.*, return to the liquid phase) when it is compressed or when its temperature is reduced.

For example, suppose a litre of air-ether mixture at 30°C. and 760 mm. of mercury, containing 2 grams of ether vapour, is compressed to half this volume. The maximum pressure that ether vapour can exert at 30°C. is 648 mm. of mercury, which is equivalent to 2·58 grams of ether per litre or 1·29 grams of ether in 500 c.c. It follows, therefore, that the 500 c.c. of compressed air-ether mixture contains (2 − 1·29) or 0·71 grams too much ether vapour, and consequently 0 71 grams of ether will condense out of the gaseous mixture, and return to the liquid state.

Or, again, suppose the temperature of a litre of saturated air-ether mixture at sea level is reduced from 30° to 20° C. At 30°C. a litre of saturated mixture contains 2·58 grams of ether vapour and at 20°C. a litre of saturated air-ether mixture contains 1·9 grams of ether vapour. With a fall of temperature from 30° to 20°C., it follows that condensation will occur, and (2·58 − 1·9) or 0·68 grams of ether vapour will return to the liquid phase.

The treatment of vapours in terms of the gas laws, therefore, reaches a limit at the vapour pressure of the fluid at a given temperature,[1] but a vapour at a given temperature, separated from its liquid or subjected to rise of temperature or to expansion—and these three conditions obtain in clinical anæsthesia—behaves as a

[1] Deviation from the ideal behaviour actually occurs before this.

true gas, and obeys the gas laws, and it can be concluded that narcotic vapours, in the conditions obtaining in clinical anæsthesia, conform to the gas laws.

Solution of Gases and Vapours. The solution of a gas in a liquid is essentially the assumption of gaseous equilibrium between the gas-liquid system, and can be explained by considering the equilibrium which exists between a pure liquid and its vapour in a closed space at a given temperature. When a liquid is thus confined, molecules escape from the liquid into the space above until the number of molecules re-entering the liquid from the vapour phase in the space above exactly equals the number of molecules escaping from the liquid into this space. When this state has been achieved, the liquid and its vapour phase are in equilibrium, for the escape tendency of molecules from the liquid is exactly equalled by the vapour pressure of its vapour phase above the liquid.

In other words, the tension of the vapour dissolved in its liquid is exactly equalled by the pressure of its vapour above the liquid, for a solution is saturated in respect to a phase of a component and not in respect to the component. Thus, water may be saturated in respect to some low pressure of ether vapour while still unsaturated in respect to liquid anhydrous ether.

Vapour pressure, or the solubility of a vapour in its liquid at a given temperature, is clearly determined by the equalization of the intermolecular forces and the kinetic effects of temperature. The solution of a gas in a liquid, at a given temperature, depends upon these same forces; for when in a gas-liquid system at a given temperature, equilibrium is achieved between the solute and the solvent, the pressure of the gas in contact with the liquid is exactly equalled by the tension exerted by this gas in solution in the liquid This is to say, the escape tendency of the gas in solution is exactly equalled by the pressure of the gas above the liquid.

The conclusion that, in the conditions obtaining in clinical anæsthesia, narcotic gases and vapours obey the gas laws permits one to anticipate the solution of narcotic gases and vapours in liquids according to Henry's Law, which states that "*the mass of gas dissolved in a given volume of a liquid at a given tempera-*

ture is proportional to the pressure of the gas in contact with the liquid."

TABLE 4.

COEFFICIENT OF SOLUBILITY IN 100 C.C. OF WHOLE BLOOD AT 37°C.

Di-ethyl-ether	1500 c.c.	Henderson and Haggard (1927).
Di-vinyl-ether	—	
Ethyl Chloride	250 c.c.	Nicloux *et al* (1934).
Acetylene	74 1 c.c.	Shoen (1923).
Nitrous oxide	41·2 c.c.	Siebeck (1909).
Ethylene	11 8 c.c.	Nicloux *et al* (1934).
Cyclopropane	1·15 c.c.	Waters (1936).
Chloroform	1·42 c c.	Wintersteín (1926).

For example, 100 c.c. of human blood at body temperature dissolves 71·5 grams of nitrous oxide when the pressure of nitrous oxide in contact with blood is 760 mm. of mercury, and the same 100 c.c. of blood dissolves half this amount (35·75 grams) when the pressure of nitrous oxide is reduced to 380 mm. of mercury.

Since, according to Boyle's Law, the volume of a given mass of gas at a constant temperature varies inversely as the pressure, an accurate picture of the solution of a gas in a liquid may be obtained by re-stating Henry's Law as: *the mass of gas dissolved in a given volume of liquid at a given temperature varies directly as the pressure of the gas, but the volume of gas dissolved is independent of the pressure of the gas, and does not vary.*

For example, when the pressure of nitrous oxide is 760 mm. of mercury, 100 c.c. of human blood at body temperature dissolves 41.2 c.c. of nitrous oxide at a tension in solution of 760 mm. of mercury and the weight of nitrous oxide in solution is 71·5 grams. When the pressure of nitrous oxide is reduced to 380 mm. of mercury, the same 100 c c. of blood dissolves 35·75 grams of nitrous oxide, but the volume of gas dissolved is still 41·2 c.c., and its tension in solution is 380 mm. of mercury, for gaseous equilibrium has been achieved when saturation is complete.

The constant volume of a gas or vapour dissolved in a given liquid or solvent, at a given temperature, is termed the *coefficient of solubility* of the gas or vapour in that solvent, at that temperature Table 4 shows the coefficient of solubility of the common anæsthetic gases and vapours per 100 c.c. of human blood at body temperature.

In gas analysis, however, it is necessary in practice to reduce the volume of gas or vapour in solution, at a given temperature and pressure, to the standard pressure of atmospheric air at mean sea level, viz., 760 mm of mercury; this is responsible for the erroneous belief present in the minds of many students of anæsthesia that the volume of gas dissolved in a liquid, at a given temperature, varies as the pressure, and it is a common experience to be told that " when the pressure of the gas is doubled, the volume of gas dissolved is doubled ".

For example, the 41·2 c.c. of nitrous oxide dissolved in 100 c.c. of blood at body temperature, when the pressure of the gas is 380 mm. of mercury, is represented in gas analysis as 20·6 c.c., at a tension of 760 mm. of mercury (Boyle's Law). While these two values represent accurately the same weight of gas in solution, the latter completely misrepresents the kinetic properties of the gas in solution, for the dissolved gas is in equilibrium with the atmosphere with which it is in contact, and its tension in solution must, therefore, be 380 mm of mercury. Moreover, this tension of 380 mm. of mercury in relation to its surroundings, indicates the direction and rate of gas movement to be anticipated; that is to say, the direction and rate of the escape tendency of the anæsthetic gas from the solution.

It can be concluded that at body temperature, and at the relatively low pressures employed in clinical anæsthetic practice, narcotic gases and vapours obey Henry's Law, and that within these limits the mass of an anæsthetic gas or vapour dissolved in blood, extracellular fluid or tissue cells, varies in an upward and downward direction as the pressure of the narcotic gas or vapour in contact with the solvent.

In clinical practice, the upper limit of the pressure of all narcotic gases is conditioned by the fact that the total pressure of the anæsthetic atmosphere at mean sea level is 760 mm. of mercury, and if it is to maintain life, this atmosphere must contain oxygen at a partial pressure of 160 mm. of mercury (circa). It follows, in clinical practice, that the greatest possible partial pressure which all anæsthetic gases can exert in the anæsthetic atmosphere is 600 mm. of mercury (circa).

Narcotic liquids such as ethyl chloride, whose boiling point is

below 20°C., in like manner, can exert a vapour pressure in the anæsthetic atmosphere of up to 600 mm. of mercury, but the upper limit of vapour pressure exerted by narcotic liquids, whose boiling point is higher than 20°C., is less than 760 mm. of mercury at mean sea level and room temperature, viz., 20°C.

TABLE 5

THE RELATION OF VAPOUR PRESSURE TO BOILING POINT.

NARCOTIC	FORMULA	BOILING POINT AT MEAN SEA LEVEL	VAPOUR PRESSURE AT 20°C. AND MEAN SEA LEVEL
Ethyl Chloride	CH_3CH_2Cl	12.5°C	> 760 mm. of mercury
Di-vinyl-ether	$(CH_2CH)_2O$	28°C	558 mm. of mercury
Di-ethyl-ether	$(CH_3CH_2)_2O$	34°C	460 mm. of mercury
Chloroform	$CH.Cl_3$	64°C	160 mm. of mercury
Trichlor-ethylene	$C.Cl_2CH.Cl$	87°C	62 mm. of mercury
Decane	$C_{10}H_{22}$	168°C	7.6 mm. of mercury

Table 5 shows the vapour pressure which the narcotic liquids in common clinical use and decane exert at 20°C. at mean sea level. It is seen that the higher the boiling point of the particular narcotic liquid, the smaller is the maximum vapour pressure it can exert in the conditions which obtain in clinical practice. In clinical practice, these vapour pressures represent the greatest possible partial pressure which each particular narcotic vapour could exert in the anæsthetic atmosphere.

There is a minimum threshold concentration for each narcotic below which it fails to produce a biological response on living cells, and the mass of a particular narcotic which must be dissolved in extracellular fluid to produce an effective concentration is determined by the potency of the particular narcotic. The ability to dissolve a given narcotic gas or vapour in blood and extracellular fluid in an effective narcotic concentration, therefore, depends upon the potency of the narcotic, upon its coefficient of solubility in these solvents, and upon the partial pressure which it is possible to exert in the anæsthetic atmosphere.

For example, *nitrous oxide* is freely soluble in blood and extracellular fluid, but it is a weak narcotic, and when it exerts a partial pressure of 600 mm. of mercury in the anæsthetic atmosphere, its concentration in blood and extracellular fluid is barely an effective concentration for the areas of sensory co-ordination of the brain. A partial pressure of 1440 mm. of mercury in the anæsthetic atmosphere would be required to dissolve sufficient nitrous oxide to depress the areas of motor co-ordination of the brain, and a partial pressure of 2280 mm. of mercury of nitrous oxide to depress the vital medullary centres of the brain. In the conditions which obtain in clinical anæsthetic practice, a partial pressure of more than 600 mm. of mercury is not possible without anoxia. The narcotic limitations of nitrous oxide must be attributed to its weak narcotic properties, and not to the physical properties of the drug. The first five narcotic liquids in Table 5 are sufficiently potent narcotics. They are sufficiently soluble in blood and extracellular fluid, and they may exert a sufficiently high vapour pressure at mean sea level and room temperature to permit them to be concentrated in blood and extracellular fluid in an effective anæsthetic concentration. If, however, the temperature of the narcotic liquid is sufficiently lowered, its vapour pressure and, in turn, the partial pressure of the narcotic in the anæsthetic atmosphere may be reduced to a level which is insufficient to dissolve the narcotic in blood and extracellular fluid in an effective concentration.

Finally, *decane*, the tenth member of the paraffin series, is a potent narcotic, but its solubility in water is so small, and its maximum vapour pressure at mean sea level and room temperature is so low (viz., 7.6 mm. of mercury) that it is not possible to dissolve decane vapour in blood and extracellular fluid in an effective narcotic concentration; in this instance, the anæsthetic inertness of the drug is to be attributed solely to its physical properties, for it is an effective narcotic.

Solution of Liquids and Solids. The solution of a liquid in a liquid, in like manner, is determined by the balance of intermolecular forces and the kinetic effect of temperature, and results in the assumption of equilibrium between the solvent and

the solute. This is achieved when the escape tendency of molecules to and from each liquid in the mixture has become equal.

For example, when two liquids are mixed, two layers are formed; the lighter liquid floats on the denser liquid, and molecules escape from the lighter to the denser layer and vice versa. The escape tendency of molecules from one layer to the other, and, in consequence, the composition of the two layers (called "conjugate pairs") depends upon their similarity, the ease with which the molecules mix, and the temperature of the mixture. The kinetic effect of rise of temperature is to increase the escape tendency of molecules from each layer until, at the critical solution temperature, the partial pressure of each component is the same in each layer. When this result has been achieved, the two layers are homogeneous, and the two fluids are in equilibrium, miscible in all proportions.

The solution of a solid in a liquid is likewise the assumption of molecular equilibrium in the solid-liquid system. Thus, when a saturated solution of a solid in a liquid is cooled, the solid is precipitated from solution until the escape tendency of molecules of the solute from solution is exactly equalled by the number of molecules gained by the solution from the precipitated solute.

Surface Tension. Dissolved substances, by altering the forces of intermolecular attraction, modify the surface tension of a liquid, and this, in turn, modifies the escape tendency of molecules from their solution in the liquid.

In a homogeneous liquid such as water, the molecules are packed within the radius of molecular attraction of adjacent molecules, and, in the interior of the liquid, molecules are attracted equally on all sides by the molecules adjacent to them and are in a state of equilibrium. The molecules at the surface of the liquid, however, are subjected to molecular attraction from within, but this force is not balanced by a corresponding attraction from without. This unbalance constitutes surface tension, which may be looked upon as a force hindering the escape tendency of molecules from the liquid.

The solution of most non-conductors and all narcotics reduces the surface tension of water, and, as Gibbs has shown, the ability to lower the surface tension increases with the molecular weight

of the dissolved substance. Moreover, the molecules of a dissolved substance which reduces the surface tension of a liquid are concentrated or adsorbed at the surface of the liquid. The surface adsorption of the solute is greatest for a solvent such as water which normally has a high surface tension, for solutes with a high molecular weight, when the solute is relatively insoluble, and when the solution is not saturated. The absolute quantity of solute condensed or adsorbed at the surface of a liquid must always be small, but any reduction of surface tension, however small, increases the adsorption of solutes at the surface of liquids.

The surface tension of a liquid may also be opposed by the attraction of a second phase in contact with the surface of the liquid. Thus, at the interface of contact between a liquid/air system, a liquid/liquid system, or a liquid/solid system, the attraction exercised on the molecules in the liquid, by the air, the liquid or the solid phase, decreases the surface tension of the liquid, and, in consequence, increases the escape tendency of molecules from the liquid into the second phase.

In a drug-cell system, therefore, the surface tension of extracellular fluid is *opposed by the attraction of the semi-solid* cell surface with which it is in contact, and on this account the surface tension of extracellular fluid is diminished, and the escape tendency of molecules from extracellular fluid to the cell surface is increased.

It can be concluded that the attraction exercised by the cell surface favours the escape of narcotic molecules from extracellular fluid to the cell surface, and that this escape tendency is further increased by the ability of narcotics to lower the surface tension, and to adsorb at the surface of extracellular fluid, which contains 90-99% of water. Such drugs are said by Traube to possess a low solution affinity or haft-druck.

Gases and vapours do not exhibit the phenomenon of surface tension, for the distance between their molecules is greater than the radius of their molecular attraction; but narcotic gases and vapours, when dissolved in a liquid such as water, reduce its surface tension. A greater decrease in the solution affinity may be expected in the case of narcotic solids, for they produce a greater decrease in surface tension because of their relatively larger

molecular weight. On this account, and also because by virtue of their narcotic potency, they act in unsaturated solutions at a relatively low concentration, and they tend to adsorb at the surface of extracellular fluid more readily than narcotic gases and vapours.

A low solution affinity, by increasing the escape tendency of narcotic molecules from extracellular fluid, will assist the uptake of narcotics by the cell and in turn will hasten the assumption of narcotic equilibrium in the drug-cell system. In so far as the uptake of a narcotic by the cell influences biological response, this physical property of the narcotic may be expected to increase the drug's intensity of action.

Traube (1904-1915) drew attention to the close relationship existing between (a) the ability of a narcotic to lower the surface tension of water and (b) its narcotic potency. It has been objected that the ability to lower the surface tension of water at a liquid/air interface is not necessarily an index of its effect at a liquid/semi-solid cell membrane interface, but Howard and Sollmamm concluded that, within the range of normal biological action, these two indices tend to vary in the same direction. In an homologous series of narcotic drugs, the ability to lower the surface tension of water does increase in parallel with the intensity of the narcotic action of successive members of the series; but other physical properties, such as boiling point, molecular weight and oil/water partition coefficient, vary in like manner. When, however, dissimilar narcotics are compared, just as was the case with the oil/water partition coefficient, it is found that the parallel between the ability to lower surface tension and narcotic potency is not an exact one. This is to be expected, for, like the oil/water partition coefficient, the ability to lower the surface tension of extracellular fluid is a physical factor which increases the escape tendency of narcotic molecules from extracellular fluid to the cell surface; but it plays no part in narcosis *per se* that is, in the fixation of the drug and the biological response of the cell to the mass of narcotic fixed.

Inasmuch as drug fixation is influenced by the uptake of drugs by the cell, this physical property will be a factor in determining the intensity of narcotic action, and when different narcotics are compared, the intensity of narcotic response will be influenced

sometimes by the ability of the narcotic to lower the surface tension of extracellular fluid, and sometimes by the oil/water partition of the drug. In actual practice, there appear to be fewer exceptions to the Meyer-Overton index than to Traube's index. For narcotic gases and vapours, the oil/water partition coefficient is a dominant physical factor; narcotic solids follow sometimes the one and sometimes the other index, probably in keeping with the molecular weight, solubility and potency of the particular narcotic liquid or solid.

It is to be emphasised that the parallelism of narcotic potency with lipoid solubility and/or surface tension phenomena does not explain narcosis. Neither of these physical properties is essential for a drug to be able to combine with cell protoplasm and produce narcosis; but as factors assisting the uptake of narcotic drugs by cells, singly or together they have a significant influence on drug fixation and so on narcotic action.

References.

1. Fuhner, H (1921) *Biochem Z.* 115, 235.
2. Henderson, Y, and Haggard, H W. (1927) "Noxious Gases," p. 144. The Chemical Catalog Co, N.Y.
3. Hermann, H H (1866). *Arch Anat. Physiol. Lpz.*
4. Hiller, S. (1927). *Proc Soc exp. Biol. N.Y.* 24, 427, 938
5. Marsland, D (1934) *J. cell comp. Physiol.* 4, 9
6. Meyer, H. H (1899). *Arch. exp. Path. Pharmak.* 42, 109.
7. Overton, E. (1901) *Studien uber die Narkose.*
8. Richet, C (1893). *C. R. Soc Biol Paris.* 54, 775
9. Traube, J (1904) *Pflüg Arch, ges Physiol.* 105, 541.

CHAPTER IV

THE UPTAKE OF NARCOTICS BY CELLS

OUR knowledge of the uptake of drugs by cells has not advanced very much beyond the original conception of Hertzog and Betzel (1911). These observers studied the uptake and distribution of various drugs by yeast cells, and they concluded that uptake was effected by one of three types of action.

1. Irreversible chemical action
2. Adsorption
3. Differential solubility

The uptake of narcotics by living cells from the extracellular fluid with which they are in contact, consists essentially in the passage of narcotic molecules from extracellular fluid to the living cell, until narcotic equilibrium has been established in the drug-cell system. The mechanism of narcotic uptake is necessarily limited to the second and/or third possibility cited by Hertzog and Betzel, for the most characteristic feature of narcosis is that it is essentially a freely reversible process.

Of these two possibilities, it is to be expected that adsorption and solubility will each play a part in the production of narcotic equilibrium in the drug-cell system, for they are manifestations of the same force, namely, the escape tendency of molecules in an effort to assume a state of equilibrium. The mechanism of uptake of narcotics is determined primarily by the physical properties of the particular narcotic; for, when the cell membrane is impermeable to the passage of a narcotic, adsorption of the narcotic on the cell surface is its only method of approach to the site of its drug fixation, and, when the cell membrane is permeable to the passage of the particular narcotic, solubility plays a dominant rôle in the assumption of narcotic equilibrium in the drug-cell system.

Adsorption. As Traube has pointed out, the concentration or adsorption of a solute at the interface between extracellular fluid and the semi-solid cell membrane is related to the ability of the

solute to lower the surface tension of the liquid phase, and an adsorbed substance may be removed from the surface of the liquid phase by a second solute, which lowers the surface tension of the liquid more powerfully than does the first solute. This physical reaction is termed " adsorption displacement ", and when several substances are present in solution, each is adsorbed less than if it was present alone in solution.

Numerous examples of adsorption displacement are available. For example, alcohol displaces acetic acid adsorbed on charcoal, and adsorbed glucose is displaced by the adsorption of ethyl urethane. Warburg (1921) showed by direct adsorption measurements that animal charcoal adsorbed less amino-acid from a mixture of amino-acid and narcotic than from a pure amino-acid solution, and that the addition of a narcotic to an amino-acid/charcoal system resulted in the liberation of the amino-acid that had been previously adsorbed. He showed, moreover, that the inhibition of the oxidation of amino-acid on charcoal, produced by the adsorption displacement of the amino-acid by the narcotics of an homologous series, was governed by the law of homologous series. This result might be expected when it is realized that the intensity of adsorption displacement depends upon the ability to lower the surface tension of the liquid phase—a property which in an homologous series increases progressively with each member of the series.

Warburg calculated, for a particular narcotic, that the adsorption constant, K, would be equivalent to the number of molecules, X, in a mono-molecular layer of the narcotic covering the active surface, multiplied by the area covered by each molecule; this area, assuming that the molecules were spherical in shape, was estimated as the two-thirds power of the molecular volume, Vm, calculated from Lorenz and Lorenz refractive indices.

Thus.

$$K = X(Vm)^{\frac{2}{3}}.$$

Substituting Freundlich's adsorption formula, $X = \alpha c^{1/n}$, where X equals the number of molecules, c equals the effective concentration and α and n are constants; then:

$$K = \alpha c^{\frac{1}{n}} (Vm)^{\frac{2}{3}}.$$

If the adsorption constant K and the molecular volume Vm of the narcotic is known, the effective concentration of the narcotic may be calculated.

TABLE 6.

THE RELATION OF THE INHIBITION OF CYSTINE OXIDATION TO THE AMOUNT OF ANÆSTHETIC ADSORBED.

DRUG	MOLAR CONC FOR EQUAL INHIBITION CYSTINE OXIDATION	X MILLI-MOLS PER GRAM OF CHARCOAL	$K = X.Vm^{\frac{2}{3}}$
Asymmetric di-methyl urea	0 03	1·1	9 0
Symmetric di-ethyl urea	0·002	0 68	6 9
Phenyl urea . . .	0 0002	0 76	8 7
Acetamide	0 17	1 2	7·3
Valeramide	0 003	0 62	6 9
Acetone	0 073	1 33	8·3
Methyl phenyl ketone .	<0 0004	0 73	8·0
Amyl alcohol ...	0 0015	0 87	7·9
Acetonitrile	0·2	1·5	7·7

Table 6, taken from Warburg's work, shows, for various dissimilar narcotics, that while the concentration necessary to inhibit the oxidation of cystine on charcoal varied a thousand-fold, this concentration, in each instance, resulted in the adsorption of a quantity of narcotic X, whose area $X(Vm)^{\frac{2}{3}}$ was, within limits, always the same. In this table of results, the greatest value is 9·0 and the smallest value is 6 9.

Warburg proved therefore, first, that the mechanism of the inhibition of the oxidisation of amino-acid on charcoal by narcotics was an adsorption displacement phenomenon—that is, the adsorption displacement of one solute, cystine, by a second solute, the narcotic; he also proved that the intensity of this physical reaction was directly proportional to the area covered by the absorbed substance, and was, therefore, independent of the chemical nature of the narcotic.

Warburg also demonstrated that respiratory enzymes on the surface of anærobic cells are inhibited by narcotics, and he assumed that this was an adsorption displacement phenomenon, and that the analogy with the cystine-charcoal system was an exact one. He therefore concluded that the action of narcotics on living cells consisted of non-specific adsorption displacement, not only of " respiratory enzymes ", but also of " innumerable other specified cell processes ". In support of this thesis, he contrasted the " non-specific anti-catalytic action " of narcotics with the specific anti-catalytic action of potassium cyanide, which combines with a particular respiratory enzyme, indophenol oxidase.

On the basis of these observations, Warburg evolved the following thesis: " If narcotic effect depends simply upon the fact that narcotics become attached to a given effective area (*of the cell surface*) by being adsorbed by this area, and by adsorption displacement displace ferments already adsorbed on this surface, then the degree of displacement, and with it the intensity of action, must be determined solely by the magnitude of the surface which is covered by the adsorbed narcotic, and is independent of the chemical nature of the substance (i.e. the narcotic)."

Keilin (1925), however, has since shown that narcosis is produced by the specific inhibition of a particular respiratory enzyme, *dehydrogenase*, and Warburg's thesis of the non-specific " blanketing effect " of narcosis therefore fails. The adsorption of narcotics to the cell surface, and the adsorption displacement of the normal substrate from thence is, in consequence, a physical property of the narcotic which hastens the assumption of narcotic equilibrium in the drug-cell system, but after concentration at the site of drug fixation in the living cell, the fixation of the narcotic depends upon the possession of particular chemical radicals in its molecule, and is a very specific phenomenon.

When the cell membrane is *impermeable* to the passage of a narcotic, the adsorption of the drug from extracellular fluid on to the cell membrane is its only method of approach to the site of its drug fixation on the cell surface. In this instance, the uptake of the narcotic by the cell is analogous to the adsorption of gases and vapours by a metal surface. The simplest condition occurs when one molecule of the narcotic unites with one specific receptor on the

cell surface, and when the drug is present in excess in extracellular fluid, so that its concentration does not change appreciably during uptake. Under these conditions, Hitchcock (1926) has stated that those equations which Langmuir used to express the adsorption of gases by a metal surface, described the uptake of such drugs by the cell surface.

Hence, if the concentration of the narcotic in extracellular fluid equals x, and is not altered significantly by the uptake of the drug by the cell, the total number of receptors on the cell surface equals *100*, and the percentage of receptors occupied by the drug equals y. Then the percentage of free or unoccupied receptors is $(100 - y)$, and equilibrium occurs in the drug-cell system when

$$Kx = \frac{y}{100 - y}.$$

When two molecules of the narcotic unite with one receptor, equilibrium occurs when

$$Kx^2 = \frac{y}{100 - y}.$$

When, however, the cell membrane is *permeable* to the passage of a narcotic, adsorption to the cell surface hastens the escape tendency of narcotic molecules from extracellular fluid to the cell surface, and their ultimate solution in the cell itself.

Permeability. In the case of relatively insoluble drugs of high molecular weight and potency it will be seen that the specific receptors or active patches, to which these drugs are adsorbed and fixed, constitute only a very small proportion of the cell surface. In discussing the uptake of such drugs by adsorption, Hitchcock postulates an *impermeable* cell membrane, and considers only the area of the cell surface occupied by these specific receptors. Warburg, in like manner, considers only " *given effective areas* " on the cell surface, and by inference ignores the bulk of the remaining cell surface.

The surface of living cells, however, is permeable to the passage of the majority of aliphatic narcotics, it is most improbable either that adsorption is the sole mechanism of uptake, or that the bulk of the cell surface can be ignored in considering the uptake of narcotics to which the cell surface is permeable.

L'Hermite (1885) attributed the ability of a drug to penetrate into the interior of living cells to the solubility of the drug in the cell membrane. The numerous observations of Overton and others have failed to show any direct relationship between the chemical constitution of a drug and its cell permeability, but Overton found that with most living cells, lipoid soluble substances penetrate more readily into the cell interior than substances which are predominantly water soluble. Traube believed that difference in the size of molecules was a factor, and Collander (1937) has shown in *Charda* that the rate of diffusion of molecules through the cell membrane depends partly on molecular volume, but that when molecules of similar size are compared, there is a clear relationship between permeability and the oil/water partition coefficient of non-*electrolytes, that is, solutions such as narcotic solutions which are* non-conductors.

In some cases, at least, the question is not so much one of absolute differences of permeability and impermeability as differences in the rate of diffusion through the cell membrane, and this, in turn, is related to molecular volume and density. L'Hermite's original thesis—that the passage of a drug through the living cell membrane depends essentially upon the solubility of the drug in the cell membrane— can be accepted as a dominant factor in the uptake of soluble narcotics by the cell membrane, and, in turn, by the cell interior, and the relationship of permeability to the oil/water partition coefficient of the drug strengthens the assumption that the cell membrane is a fat/water surface composed of lipoid and protein

It is a well known fact that narcotics, above a certain critical concentration, act as hæmolytics, and this effect is produced by an irreversible alteration in the cell membrane, which becomes more permeable than normal to water. This critical hæmolytic concentration is higher—but not very much higher—than the maximum narcotic concentration. At a narcotic concentration, however, an anti-hæmolytic effect is produced which is freely reversible, and this is attributed by Arrhenius and Bubanovic (1919) to a prolongation of the water penetration into the cell.

Hober suggested, and Lillie (1909-1916) showed, that narcotics decrease the permeability of the cell membrane; and this work

led to the "PERMEABILITY THEORY OF NARCOSIS." This theory postulates that all factors in any way decreasing the permeability of the cell membrane lower the excitability of the cell, and that narcotics, by their accumulation in the lipoid of the cell membrane, decrease permeability and so produce narcosis. Lillie (1909) suggested that carbon dioxide elimination is hindered in this way, but neither the *diffusion of carbon dioxide* (*Winterstein, 1926*), nor the diffusion of oxygen (Meyerhoff, 1912) is reduced, and there is no change in the solubility of gases such as Mansfield has suggested, for neither chloroform (Moore and Roaf, 1904), nor a strong solution of chloral hydrate (Knopp, 1904) diminishes the solubility of gases. Winterstein (1926) agrees with the thesis of Hober and Lillie, but denies the importance of lipoids, and lays stress on the reduced permeability of the cell membrane to "unspecified water soluble constituents which are indispensable for certain vital processes"! *There is no proof, however, that* changes in the permeability of the cell membrane are related in any way with the production of the state of narcosis, and it is proposed to consider permeability solely in terms of uptake.

In a drug-cell system in which the cell surface is permeable to the passage of narcotics, narcotic molecules escape from one solvent, extracellular fluid, into the second solvent, the cell surface, and any physical property of the narcotic—such as the ability to lower the surface tension of extracellular fluid and to adsorb at the fluid-cell interface, or the ability of the narcotic to dissolve freely in cell lipoids—will hasten the uptake of the narcotic in *the cell membrane*. The solution of the narcotic in the cell membrane, in turn, will be followed by the escape of narcotic molecules from thence into a third solvent, *the cell interior*, which, as Hill (1931) has demonstrated, may be looked upon as a water phase, free to dissolve in a normal manner solutes added to it.

The uptake of the soluble narcotics by living cells will be complete when equilibrium, in respect to the narcotic, has been achieved in the drug-cell system; when, in fact, the tension of the narcotic gas or vapour, or the concentration of the narcotic liquid or solid, is equal in extracellular fluid, the cell surface and the cell interior. The uptake of such a narcotic by living cells is thus a differential solubility process, and, as Meyer's third postulate

states, the narcotic is partitioned between the cell lipoid and the remaining cell constituents which are mainly water.

The solution of narcotics in the cell interior was said by Claude Bernard to produce a reversible coagulation of the cell protoplasm which produced narcosis W. D. Bancroft (1931) adduces new arguments in support of this "COAGULATION THEORY OF NARCOSIS," but two facts stand out: flocculation is produced at higher concentrations than that of anæsthesia, and coagulation is an irreversible process. Since, in addition, narcotics act in a specific manner on the cell surface, and not in the cell interior (Hiller, 1927, Marsland, 1934), this intracellular coagulation, when it occurs, must be looked upon as a deleterious side-action, produced by too great a concentration of the narcotic in solution in the cell interior.

The evidence discussed indicates that the uptake of narcotics by living cells is a physical process which aims at creating a state of equilibrium, in respect to the narcotic, in the drug-cell system, and the mechanism of uptake of a particular narcotic by living cells is determined by its physical properties. On the one hand, the impermeability of the cell surface to insoluble narcotics of high molecular weight and potency makes it probable that the uptake of such narcotics is an adsorption process; and, in this case, the concentration of the narcotic at the site of its drug fixation in the cell surface will vary as the logarithm of its concentration in extracellular fluid On the other hand, the permeability of the cell surface to soluble narcotics, whose water solubility is adequate and whose oil/water partition coefficient is greater than unity, makes it probable that the uptake of such narcotics by living cells is a differential solubility process; and, in this case, the concentration of the narcotic at the site of its drug fixation in the cell surface will vary directly as its concentration in extracellular fluid.

Direct Experimental Evidence of the Uptake of Narcotics by Cells. Direct experimental evidence of the nature of the uptake of narcotics by living cells is scanty and inconclusive It is based upon the mass of narcotic absorbed by the living cell in response to a given concentration of the narcotic in the extracellular fluid with which it is in contact. The ratio

$$\frac{\text{mass of narcotic absorbed by the cell}}{\text{concentration of narcotic in extracellular fluid}}$$

is called the *Distribution Coefficient*, and uptake may be represented by the following formula:

$$K \cdot c^n = X.$$

Where c equals the concentration of the narcotic in extracellular fluid, X equals the mass of narcotic taken up by the cell when equilibrium has been achieved. K is a constant which depends upon the nature of the solute and the solvent, that is, the narcotic, on the one hand, and the particular type of cell, on the other; n is a constant which depends upon the character of uptake.

When n equals unity, X will vary directly as the concentration c. That is to say, the uptake of the narcotic by the cell is directly proportional to the concentration of the narcotic in extracellular fluid. In this instance, the distribution coefficient will remain the same for any concentration of the narcotic in extracellular fluid, and the uptake of the narcotic by the cells obeys Henry's Law, and is a simple *differential solubility mechanism.*

If the value of n is less than unity, the mass of narcotic taken up by the cell when equilibrium has been achieved will vary as some power of the concentration in extracellular fluid less than unity. In this instance, the distribution coefficient will decrease progressively and in an exponential manner, as the concentration of the narcotic in extracellular fluid is increased. This type of uptake is characteristic of an *adsorption mechanism.*

Finally, when the value of n is greater than unity, the distribution coefficient will progressively increase, as the concentration of the narcotic in extracellular fluid is increased. This mechanism is interpreted as a *differential solubility process with polymerisation of the narcotic*

And in the interpretation of the following results, according to current opinion:—

1. True adsorption is indicated when the distribution coefficient falls with the rise of concentration in extracellular fluid.

2. Simple differential solubility is indicated when the distribution coefficient remains constant for all concentrations.

3. Differential solubility with polymerisation is indicated when the distribution coefficient increases with rise in the concentration of the narcotic in extracellular fluid.

Loewe (1912) observed that the partition coefficient of chloroform in a brain/chloroform water system decreased as the concentration of chloroform in the water increased. This indicated an adsorption process. On the other hand, Moore and Roaf (1904, 1906), who studied the uptake of chloroform by serum, heart muscle, brain and liver tissue emulsions, found that the distribution coefficient of chloroform between these various tissues and normal saline remained constant over a range of low concentrations of chloroform in saline. This indicated a simple differential solubility process. With increase of the concentration, however, a *critical concentration was reached, when opalescence and precipitation of proteins occurred, and, with the appearance of this* phenomenon, the distribution coefficient increased.

Hertzog and Betzel (1911) observed this same result with the uptake of chloroform by yeast cells. This precipitation of protein is an irreversible process, associated with an alteration in the collodial condition of the serum and/or the cell protoplasm; the concentration necessary to produce it is greater than the maximal anæsthetic concentration (*cf.* page 70). Loewe and Moljawko-Wyssotski (1926), who studied the uptake of narcotics by muscle and nerve pulp, observed a swelling of the tissues with narcotic uptake, and considered it a source of error similar to that of precipitation

Storm van Leeuwin and Le Heux (1919) found no change in the distribution coefficient of chloroform, and Leuze (1922) obtained a similar result with bromoform.

Warburg (1914) asserts that the distribution coefficient of acetone remains unchanged through variations of over a hundredfold in the concentration of the drug in extracellular fluid. Arrhenius and Bubanovic (1913) observed no change in the distribution coefficient of acetone and amyl alcohol, but they found that the index increased in the case of methyl and ethyl alcohol, both of which, however, are reactive.

Winterstein (1926) states that the partition coefficient of ethyl urethane between frogs and the water in which they are immersed remains constant with a two-fold increase in the concentration of the drug in this water.

It may be inferred from this evidence that, within a range of low concentrations, the uptake of chloroform is a simple differential solubility process, and that acetone, bromoform, amyl alcohol and ethyl urethane follow the same uptake process.

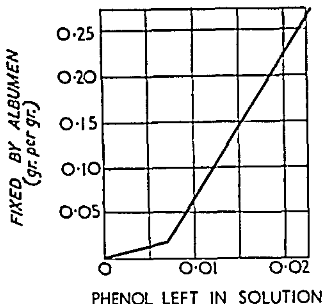


FIGURE 5.
Combination of phenol with egg albumen (Cooper, 1912)

Reichel (1909), Hertzog and Betzel (1912), and Cooper and his associates (1912-1928) have shown that the distribution coefficient of phenol between extracellular fluid and protein, or cells such as yeast cells, remains approximately constant until a certain critical concentration is reached, when an irreversible precipitation of protein occurs with a sharp rise of the distribution coefficient

Cooper showed that the uptake of phenol by protein is a simple differential solubility process until a concentration of 0·8% has been reached, when precipitation of protein abruptly occurs, and the distribution coefficient just as abruptly commences to increase. This rise in the distribution coefficient might well be attributed to a differential solubility with polymerisation, but Cooper found that phenol was more soluble in precipitated protein than in native protein; the distribution of phenol between native protein and water being 3/1, and the index in the case of precipitated, or denatured, protein being 10/1.

There is reason to suggest, therefore, that the uptake of phenol is a simple differential solubility process throughout, and that the increase in the distribution coefficient is due to an increase in solubility of phenol in denatured protein, and not to polymerisation of the phenol molecule.

The protein precipitation and rise of the distribution coefficient which Moore and Roaf observed with chloroform may be held to be exactly comparable with that which occurs with phenol. The critical precipitation concentration of chloroform is above that of its maximal anæsthetic concentration, and precipitation of protein must be looked upon as a deleterious side-action of this anæsthetic, and not connected, *per se*, with narcosis. The absence of protein precipitation over a hundredfold range of concentrations of acetone is significant, for prolonged exposure to this drug does not produce degeneration of cell protoplasm (*cf.* page 28).

Warburg and Weissel (1912) observed that the distribution coefficient of thymol in normal saline and the red blood corpuscles of birds diminished with rise in the concentrations of the thymol in extracellular fluid. Usui (1912), using more exact methods, observed a fall from 6 7 to 6·4 in the distribution coefficient when the concentration doubled, and from 7·4 to 6·4 when the concentration was quadrupled. This indicates an adsorption process, but Winterstein (1926) considers these differences to be too small to have any certain significance.

Usui (1912) then compared the uptake of thymol by intact red blood corpuscles of birds with the stromata of these corpuscles after laking, and also with defatted stromata. He concluded that the uptake of thymol was due to the three following factors: differential solubility between extracellular fluid and the water cell phase; fixation by the soluble cell constituents (mainly lipoids); and fixation by non-lipoid solvent cell constituents.

Dorner (1914) in a similar experiment found that the distribution coefficient of octyl alcohol was about 60 in the case of laked blood corpuscles of birds; after the stromata had been defatted it fell to 26.

These observations of Usui and Dorner confirm the view advanced by Meyer (1899) in his third postulate, namely, that

the water phase and the lipoid phase of the cell both exercise a decided influence on the uptake of narcotic drugs. In respect to the uptake of narcotics by cell stroma, Warburg advanced the thesis that cells consisted of a solid and a water phase, and he concluded that the value of the partition coefficient, cell substance/surrounding media, depended on whether solution in the water phase, or adsorption to the solid stroma, dominated.

There is, however, nothing to warrant ignoring the solubility of the narcotic in the lipoid cell phase; on the contrary, there is much to suggest, as has already been seen, its importance as a factor in the uptake of narcotics by living cells.

In respect to the influence of the cell stroma on uptake, it must be emphasized that adsorption to solid stromata after it has been subjected to a defatting process, as in the experiments of Usui and Dorner, cannot be comparable in any way with the uptake of a narcotic by the stroma of a living cell. The relatively large uptake by defatted stromata in Dorner's experiment may be attributed, either to increased adsorption due to dispersal with consequent increase of the surface area of the exposed stromata, or to an increased solubility due to its denaturation, for it will be remembered that Cooper found the solubility of native protein to rise from 3 to 10 when denaturation was produced.

The absorption of ether vapour by blood *in vivo* and *in vitro* was considered by Haggard (1923-1924) to obey the gas laws with sufficient accuracy to ensure that the observed mass of ether solved was directly proportional to the concentration of ether to which the blood or the experimental animal was exposed.

Widmark (1919) drew the same conclusion with regard to acetone, and he calculated from Nicloux data that chloroform followed the same uptake process. Schoen and Sliwka (1923-1924) came to the same conclusion with regard to acetylene, and since these gases and vapours obey Henry's Law at low concentrations, it can be concluded that at low concentrations, their uptake mechanism is a differential solubility process.

It is significant that Haldane's work, in connection with the problems of deep sea diving, on the saturation and desaturation of the body with nitrogen, was based upon the assumption that the capacity of a particular type of body tissue to absorb this gas

depended upon the lipoid/water content of the tissue, and the oil/water partition coefficient of the gas. The years of usefulness of Haldane's work emphasize the probability that his assumption was, in fact, a correct one, and points to differential solubility as the uptake mechanism of nitrogen, which is a non-reactive gas with an oil-water partition coefficient of 5·3. Since the anæsthetic gases and vapours in common clinical use are also non-reactive in character, it is reasonable to assume that their uptake mechanism is also a differential solubility process.

The observations of Gumtow (1904), Holscher (1906), Tissot (1906), Nicloux and his associates (1906) on chloroform, and that of Hansen (1925) on alcohol, acetone, ether and chloroform, all suggest that the absorptive capacity of a particular type of tissue for a specific narcotic varies in keeping with the lipoid/water content of the particular tissue, and the oil/water partition coefficient of the specific narcotic. It can be rightly objected, in many of the experiments quoted, that full saturation throughout the body had not been attained, but in spite of this valid objection, general conclusions of value can be deduced.

Nicloux (1906)found that the chloroform content of adipose tissue, after prolonged exposure, was higher than that of other types of body tissues Nicloux and Yovanovitch (1924) observed that the chloroform content of peripheral nerves, such as the vagus, the phrenic and sympathetic ganglia, which possess a high lipoid content, was higher than that of all other organs. Hansen (1925) found the content of alcohol 1/8, acetone 3/5; ether 3; and chloroform 12 times as great in adipose tissue, which contains 96% of lipoid, as in blood, which contains 2·59% of lipoid, and 79 1% of water. He concluded that the anæsthetic content was lowest in adipose tissue for substances such as acetone and alcohol, which are poorly soluble in fat but freely soluble in water; and highest for substances such as chloroform, which is poorly soluble in water but freely soluble in fat. Ether occupies a position midway between these two extremes.

Frinson and Nicloux (1907) observed that the white matter of the central nervous system, which contains 18 5% of lipoid and 70 7% of water, always contains a higher chloroform content than that of grey matter, which contains 7 4% of lipoid and 83 4%

of water; and Hansen (1925) found with alcohol, which is a predominantly water soluble narcotic, that the alcohol content of grey matter was higher than that of white matter, a result which is in keeping with the water content of these two types of tissues.

Nicloux (1906) found that the chloroform content of the spinal cord, which contains 18% of lipoid and 74% of water, was 1½ times greater than that of whole brain substance, which contains 12.8% of lipoid and 76.4% of water.

Gumtow (1904), Holscher (1906), Tissot (1906) and Hansen (1925) all observed that the chloroform content of the medulla, whose lipoid water content is similar to that of the spinal cord, was greater than that of the cerebrum; and Hansen established the same relationship with ether. Hansen, moreover, observed that the alcohol content of the medulla was less than that of the cerebrum, and these results are again in keeping with the lipoid water content of the tissues, and the oil/water partition coefficient of the narcotics reviewed.

On the other hand, Gumtow, Holscher, Tissot and Hansen report that the chloroform content of blood, which contains 2·59% of lipoid and 79·1% of water, was greater than that of whole brain. This result is probably due to full saturation not being attained in brain tissue. Hansen, however, found, in the case of the water soluble narcotic acetone, that the blood content was greater than that of whole brain, and with the relatively greater fat solvent, ether, that it was less than that of whole brain, a result which is in agreement with the lipoid/water content of these two types of tissue.

When we consider narcotics which are soluble in the cell surface, and can, therefore, penetrate into the cell interior, there is a mass of direct and indirect evidence to suggest that at low concentrations, the mechanism of narcotic uptake is a simple *differential solubility process* In this instance, narcotic uptake obeys Henry's Law, and the mass of drug dissolved in the cell varies directly as the pressure of the gas or vapour in contact with the cell and much direct and indirect evidence has been discussed which suggests that the capacity of a particular cell to dissolve a specific narcotic depends upon both the lipoid/water

depended upon the lipoid/water content of the tissue, and the oil/water partition coefficient of the gas. The years of usefulness of Haldane's work emphasize the probability that his assumption was, in fact, a correct one, and points to differential solubility as the uptake mechanism of nitrogen, which is a non-reactive gas with an oil-water partition coefficient of 5·3. Since the anæsthetic gases and vapours in common clinical use are also non-reactive in character, it is reasonable to assume that their uptake mechanism is also a differential solubility process.

The observations of Gumtow (1904), Holscher (1906), Tissot (1906), Nicloux and his associates (1906) on chloroform, and that of Hansen (1925) on alcohol, acetone, ether and chloroform, all suggest that the absorptive capacity of a particular type of tissue for a specific narcotic varies in keeping with the lipoid/water content of the particular tissue, and the oil/water partition coefficient of the specific narcotic. It can be rightly objected, in many of the experiments quoted, that full saturation throughout the body had not been attained, but in spite of this valid objection, general conclusions of value can be deduced.

Nicloux (1906)found that the chloroform content of adipose tissue, after prolonged exposure, was higher than that of other types of body tissues. Nicloux and Yovanovitch (1924) observed that the chloroform content of peripheral nerves, such as the vagus, the phrenic and sympathetic ganglia, which possess a high lipoid content, was higher than that of all other organs. Hansen (1925) found the content of alcohol 1/8; acetone 3/5; ether 3; and chloroform 12 times as great in adipose tissue, which contains 96% of lipoid, as in blood, which contains 2 59% of lipoid, and 79 1% of water. He concluded that the anæsthetic content was lowest in adipose tissue for substances such as acetone and alcohol, which are poorly soluble in fat but freely soluble in water; and highest for substances such as chloroform, which is poorly soluble in water but freely soluble in fat. Ether occupies a position midway between these two extremes

Frinson and Nicloux (1907) observed that the white matter of the central nervous system, which contains 18 5% of lipoid and 70 7% of water, always contains a higher chloroform content than that of grey matter, which contains 7 4% of lipoid and 83·4%

The concept of an ideal solution offers advantages similar to those conferred by the conception of an ideal gas. Henry's Law describes the behaviour of gases in an ideal solution, and Raoult's Law—which is Henry's Law expressed in terms of the mole fraction—is a limiting law for solvents regardless of the nature of the solute, and can, therefore, be used to express the behaviour, not only of gases and vapours, but also of liquids and solids.

At low concentrations of the solute most solutions conform to the ideal, and obey Henry's and Raoult's Law, but at higher concentrations, because of the crowding together of molecules, the van der Waals effect may reach significant proportions, and, on this account, the deviation from the ideal may be very large. This deviation from the ideal may be a *positive* or a *negative* deviation. When the observed mass of a gas or a vapour in solution is greater than that calculated for the ideal solution, this is a positive deviation. In respect to the solubility of solids, a positive deviation from Raoult's Law corresponds to a smaller solubility, and a negative deviation to a greater solubility than that calculated from the melting and fusion points of the solid.

Solutions in which adsorption at the surface is large, deviate most from the ideal behaviour, and solutes which adsorb at the surface, and produce a large decrease in surface tension, generally show a positive deviation from ideal behaviour. At higher concentrations, therefore, narcotics tend to deviate in a positive manner from ideal behaviour, for, as Traube has shown, they have a low haft-druck. In consequence of this, at high concentrations, the mass of narcotic dissolved in the cell, when equilibrium has been assumed in the narcotic/cell system, will be smaller than that calculated according to Henry's or Raoult's Law, and as the concentration of the narcotic in extracellular fluid increases, the distribution coefficient of the narcotic will diminish.

For example, when two liquids, such as water and olive oil, are mixed, they deviate enormously from Raoult's Law, for they are practically insoluble in one another; and when a solute is added to such a mixture, its behaviour in each solvent will be quite different. If the solute conforms to the ideal, and obeys Raoult's Law in respect to one solvent, water, it will deviate greatly from

content of the cell and the oil/water partition coefficient of the specific narcotic.

At higher concentrations of the narcotic, if the current interpretation of the observed facts is accepted, the uptake of soluble narcotics from extracellular fluid by living cells is sometimes a differential solubility process with polymerisation, and sometimes an adsorption process.

The observations of Moore and Roaf, Hertzog and Betzel, and Loewe with chloroform, and those of Cooper with phenol, suggest that the increase in the distribution coefficient with increased concentrations, which has been interpreted as differential solubility with polymerisation, is in fact a simple differential solubility process, and that the increase in the distribution coefficient is due to the irreversible alteration of cell protein and the rise in solubility which accompanies its denaturation.

In respect to the diminution of the distribution coefficient with higher concentrations, which has been interpreted as an adsorption process, it is difficult to accept the view that a drug which is soluble in the cell membrane, by reason of its water and/or its fat solubility, should adsorb on the cell surface rather than dissolve in the cell membrane, penetrate and dissolve in the cell interior.

The facts as stated appear to deny the adsorption thesis in the case of soluble narcotics; moreover, Traube has pointed out that a low haft-druck is an aid, and not a hindrance, to the solution of narcotics in the cell surface, and, in turn, in the cell interior. Warburg's thesis was based on the analogy of the cystine/charcoal system, and has not yet been confirmed in the living cell. The available evidence all points to the fact that soluble narcotics do penetrate into the cell interior; and the coagulation of protein, which occurs with relatively high concentrations of chloroform, demonstrates without doubt that this is the case.

If the view is accepted that the uptake of soluble narcotics by living cells is a simple solubility process, it is possible to explain the diminished distribution coefficient that occurs with high concentrations in a manner in keeping with the accepted behaviour of dissolved substances.

adsorption process, and the mass of such a narcotic absorbed by the cell *varies as some power of its concentration in extracellular fluid less than unity*, and it can be concluded that the character of the uptake of narcotics by living cells is determined by the physical properties of the particular narcotic.

References

1. Arrhenius, S., and Bubanovic, F. (1913). *Nobel Instit.* 2 Nr. 32.
2. Bancroft, W. D., and Richter, G. H. (1931). *J. Phys. chem.* 35, 215.
3. Collander, R. (1937). *Trans. Faraday Soc.* 33
4. Cooper, E. A. (1912). *Bio chem. J.* 6, 362.
5. Cooper, E. A., and Woodhouse, D. L. (1923). *Bio chem. J.* 17, 600.
6. Dorner, A. (1914). *S. B. heidelberg Akad. Wiss.* 5b Abt. 1.
7. Frisson, M., and Nicloux, M. (1907). *C. R. Soc. Biol. Paris* 62, 1153
8. Gemtow, A. (1906). *Inaug. Diss. Geissen.*
9. Haggard, H. W. (1923). *J. biol. Chem.* 55, 131.
   (1924). *J. Biol. Chem.* 59, 737, 753, 795.
10. Hansen, K. (1925). *Skand. Arch. Physiol.* 46, 315.
   (1925) *Zur Theorie der Narkose.*
11. Hertzog, R. A., and Betzel, R. (1911). *Hoppe-Seyl. Z.* 74, 221.
12. Hill, A. V. (1931). "Adventures in Biophysics." Univ. Penn. Press.
13. Hiller, S. (1927). *Proc. Soc. exp. Biol. N.Y.* 24, 427, 938
14. Hitchcock, D. I. H. (1926). *J. Amer. Chem. Soc.* 48, 2870
15. Hotschek, F. (1906). *Inaug. Dis. Geissen.*
16. Keilin, D. (1925). *Proc. roy. Soc.* 98, 312.
17. Knopp, W. (1904). *Z. phys. Chem.* 48, 97.
18. Leeuwin, W. Storm van, and Le Heux, J. W. (1919). *Pflüg. Arch. ges. Physiol.* 177, 250
19. Leuze, E., (1922). *Arch. exp. Path. Pharmak.* 95, 145
20. Lillie, R. S., (1916). *Biol. Bull.* "Wood's Hole." 30, 311.
   (1909) *Amer. J. Physiol.* 24, 14.
21. Loewe, S., Quoted from Winterstein, H. (1926). *Die Narkose.* p. 249. Julius Springer, Berlin.
22. [illegible] *Biochem. Z.* 206, 194.
23. [illegible]
24. [illegible] 42, 109
25. Meyerhoff, O. (1912). *Pflüg. Arch. ges. Physiol.* 149, 250.
26. Moore, B., and Roaf, E. (1904). *Proc. roy. Soc. B.* 73, 382.
   (1906) *Proc. roy. Soc.* 77, 86.
27. Nicloux, M. (1906). *C. R. Soc. Biol. Paris.* 60, 206, 1153.
28. Nicloux, M., and Yovanovitch, A. (1924). *C. R. Soc. Biol. Paris.* 91, 1285.
29. Reichel, H. (1909). *Biochem. Z.* 22, 149
30. Schoen, R., and Sliwka, G. (1923). *Hoppe-seyl. Z.* 131.
31. Tissot, J. (1906). *J. Physiol. Path. gen.* 8, 417.
   (1906). *C. R. Soc. Biol. Paris.* 8, 442.
32. Usui, R. (1912). *Hoppe-seyl. Z.* 81, 175.
33. Warburg, O. (1914). *Ergebn. Physiol.* 14, 253
   (1921). *Biochem. Z.* 113, 257.
34. Warburg, O., and Weissel, R. (1912). *Pflüg. Arch. ges. Physiol.* 144, 465
35. Winterstein, H. (1926). *Die Narkose.* p. 207, 250, 252. Julius Springer, Berlin
36. Widmark, E. M. P. (1919). *Acta med. scand.* 52, 87.

the ideal behaviour in respect to the other solvent, olive oil, and vice versa.

Suppose ethyl alcohol, which has an oil/water partition coefficient of 0 046, is brought into contact over a range of vapour pressures, with a mixture containing 20% of olive oil and 80% of water. The lipoid/water content of the spinal cord is 20% of lipoid and 78% of water (circa). In this system alcohol vapour will conform to the ideal solution, and obey Raoult's Law in respect to the water phase of the mixture throughout, but at a high vapour pressure, it will deviate greatly and in a positive manner from ideal behaviour in respect to the olive oil phase of the mixture. At low vapour pressures, the solubility of ethyl alcohol in this mixture will, therefore, conform closely to Henry's and Raoult's Law, but as the vapour pressure is increased, positive deviation from ideal behaviour in respect to the oil phase reduces the solubility of alcohol in the mixture, and the distribution coefficient, therefore, decreases.

When this mixture is exposed to chloroform vapour, which has an oil/water partition coefficient of 60, a similar result will be obtained. In this instance, chloroform conforms to ideal behaviour in respect to the olive oil phase of the mixture throughout, but it deviates in a positive manner, as its vapour pressure rises, in the water phase. Hence, at a low vapour pressure, the solubility of chloroform in this mixture will conform closely to Henry's and Raoult's Law, but will deviate in a positive manner at high vapour pressures, and the distribution coefficient will decrease as the vapour pressure rises.

If tissue cells are considered as a lipoid/water system, there is reason to believe, therefore, that the uptake of narcotics to which the cell surface is permeable is a simple differential solubility process. Most narcotics which are suitable for use as anæsthetics belong to this group of narcotics, and over the low range of pressure used in clinical anæsthetic practice, *it can be concluded* that the uptake of these narcotics by living cells *obeys* Henry's Law, and the mass of narcotic absorbed by the cell *varies directly* as the pressure of the gas or vapour, and the concentration of the liquid or solid in extracellular fluid. The uptake of insoluble narcotics, to which the cell surface is relatively impermeable, is an

A study of the electrical conductivity of cells indicates that the ions in the cell interior are in true solution, and Hill (1931) concluded that nearly the whole of the water of muscle is "*free*," in the sense that it can in a normal manner dissolve substances added to it. Hill and Kupalov (1930) showed that only a negligible proportion of the potassium within the muscle fibres of frogs could be osmotically inactive, and Botzer and Cole (1935), working on the internal conductivity of frog's muscle, found no un-ionised potassium compounds within the fibres.

Whatever the organization of the protoplasm of the cell, there is reason to believe that the cell interior contains a solution of salts in water, and that these salts are in true solution. They are not adsorbed or combined, and are capable of conducting electricity and exerting osmotic pressure.

The ionic compositions of cell protoplasm and of the fluid surrounding the cell are, however, quite different. For example, muscle cells contain more potassium than sodium, while the reverse is true of the fluid which surrounds the cells. When the vacuole of a water plant, such as Valonia, is examined, its content is found to differ completely from the water in which the plant lives; working on small cells, Heilbrunn (1936) showed similarly that the viscosity of the protoplasm of invertebrate eggs was greater than that of the fluid surrounding the eggs. These facts suggest that animal and vegetable cells, whether their protoplasm is organized in a fluid, or in a semi-rigid or rigid form, are separated from their extracellular fluid by a barrier which is relatively impermeable to the passage of ions, even ions as small as those of potassium or sodium; it is convenient, and at the same time reasonable in the light of this evidence, to call this barrier the cell membrane.

The Cell Membrane. Martin Fischer denied the presence of a cell membrane, but the process of formation and repair of the limiting membrane of cells has been observed at an injured point during micro-injection experiments. Chambers (1926) has shown that the torn surface of the echinnoderm egg is reformed when the surrounding fluid contains calcium, and he observed, when the surrounding fluid lacked calcium, that the limiting membrane does not reform and that the protoplastic content of the egg escapes.

CHAPTER V

THE FIXATION OF NARCOTICS BY ENZYMES AND CELLS

THE importance of chemical regulation in organic life was recognised by Starling soon after the discovery of hormones, and the modern concept is that many, if not most, of the functions of the body are initiated and regulated by chemical means. Modern pharmacology seeks to discover how the functions of living organisms may be modified by chemical substances, and its study must be prefaced by an adequate knowledge of the functions of the normal organism and the physiochemical reactions which occur during its normal life.

But there are many gaps in our knowledge of normal physiology and biochemistry, and when to this is added the difficulty of interpreting the action of a chemical agent on living tissues, it will be realised that modern pharmacology deals with logical probabilities rather than with formal proofs. If logical probabilities regarding the mode of fixation and action of narcotic drugs on enzymes and living cells are to be deduced, it is necessary to review briefly the present conception of the organization of the living cell.

The Cell. In many small unicellular organisms, a considerable proportion of the cell protoplasm is organized in a fluid state. Marsland (1934) concluded that the protoplasm of an amœba was organized in a fluid state, for he found that when aqueous media were injected into the amœba, they mixed freely with the cell content, but that when globules of non-aqueous media were injected, these did not mix, but could move freely in the cell interior. This conclusion agrees with that of Chambers and Reznikoff (1926) who showed, when a relatively large volume of water was injected into amœba, that the water immediately diffused throughout the cell. On the other hand, the protoplasm of muscle cells is organized in a semi-rigid state, and in the vegetable kingdom protoplasm is organized in a rigid form.

pressure and that of the fluid which surrounds it. The osmotic pressure inside and outside a muscle cell is the same, but a small independently living protozoon maintains an internal osmotic pressure which is much greater than that of the water in which it lives, and it appears that the structure of the cell membrane varies with the specific function of the particular cell. The physical structure of the cell membrane is at present a matter for conjecture, but all the authorities quoted find reason to suppose that it is composed of *lipoids*, and most agree that *protein* is also present.

Organization of the Cell Membrane. The acceptance of this view of the structure of the cell membrane makes it pertinent to ascertain how proteins react with chemical agents.

Proteins are built up of polypeptide chains and a protein molecule is made up of hundreds of these chains. In a protein gel the polypeptide chains are orientated in the form of a lattice, and it is a striking characteristic of a protein gel that it can absorb water which is held in the interstices between the lattice pattern of the polypeptide chains. Thus, 100 grammes of dry gelatine can absorb 850 c.c. of water. Chemical agents react with a protein gel in a very complex manner, and may be fixed in at least three ways. Chemical substances, with molecules too large to penetrate the lattice of the polypeptide chains, may be adsorbed on the surface, and molecules, small enough to penetrate the lattice pattern, may be loosely combined in a neben-valence, or firmly combined in a haupt-valence.

If the cell protein is orientated at the cell surface, the number of chemical combining groups, or free side-chains, is very large. It has been calculated that a small coccus whose volume is 0·25 cubic micra, contains about 2% of nitrogen, which is in turn equivalent to about 12% of protein. If this protein has molecular weight of 36,400—that of egg albumen—then each coccus contains more than 10^6 protein molecules, which is a little more than is necessary to form a mono-molecular layer of protein molecules round the surface of the coccus. It is probable, in the case of the coccus, that the greater proportion of its contained protein is orientated at the cell surface.

Cohn (1925) has calculated that a molecule of egg albumen

The micro-injection of drugs into the interior of living cells also lends weight to the thesis of a cell membrane. Brindley (1928) showed that amœba proteus was killed when immersed for twenty-four hours in N/3000 solution of hydrogen cyanide, but that the micro-injection of N/100 hydrogen cyanide into the cell interior produced no more effect than the intracellular injection of distilled water. Moreover, amœba, which had received an intracellular injection of N/100 hydrogen cyanide without harm, were afterwards killed by immersion in N/3000 hydrogen cyanide in the same manner as a normal amœba. Brindley (1928) obtained the same result in amœba with sulphurreted hydrogen, and Hiller (1927), and Marsland (1934) found that amœba dubia immersed in a narcotic solution were paralysed in a characteristic fashion, but that narcotics injected into the interior of these cells produced not narcosis, but the local coagulation of protoplasm.

These observations indicate that the cell membrane is in fact an entity, and that drugs such as ions, narcotics, cyanides etc., exert their specific pharmacological action on cells such as amœba either in or on the cell surface: *on the cell membrane* and *not* in the interior of cell The speed with which narcotics produce their characteristic biological response when present in an active concentration strengthens the view that narcotics act on the cell surface.

The Structure of the Cell Membrane. The structure of the cell membrane is still a controversial matter, and the following views have been advanced to explain its structure.

Cowles (1916) suggested that the cell surface consisted of a fat-water emulsion Heilbrunn (1936) concluded that it was composed of lipoids in combination with proteins, and Danielli and Harvey (1934) reached the same conclusion Danielli and Davson (1934) thought that the cell surface consisted of a film of lipoids covering the protoplasm with a film of protein superimposed on the lipoid film, and Rideal (1937) suggested that the cell surface was probably composed of a mixed film of protein, cholesterol and lipoids such as, for example, sphingo-myelin.

It would be a mistake, however, to imagine that the cell membrane of all types of cells was identical in structure. Thus, a red blood corpuscle cannot resist any difference between its osmotic

pressure and that of the fluid which surrounds it. The osmotic pressure inside and outside a muscle cell is the same, but a small independently living protozoon maintains an internal osmotic pressure which is much greater than that of the water in which it lives, and it appears that the structure of the cell membrane varies with the specific function of the particular cell. The physical structure of the cell membrane is at present a matter for conjecture, but all the authorities quoted find reason to suppose that it is composed of *lipoids*, and most agree that *protein* is also present.

Organization of the Cell Membrane. The acceptance of this view of the structure of the cell membrane makes it pertinent to ascertain how proteins react with chemical agents.

Proteins are built up of polypeptide chains and a protein molecule is made up of hundreds of these chains. In a protein gel the polypeptide chains are orientated in the form of a lattice, and it is a striking characteristic of a protein gel that it can absorb water which is held in the interstices between the lattice pattern of the polypeptide chains. Thus, 100 grammes of dry gelatine can absorb 850 c c. of water. Chemical agents react with a protein gel in a very complex manner, and may be fixed in at least three ways. Chemical substances, with molecules too large to penetrate the lattice of the polypeptide chains, may be adsorbed on the surface, and molecules, small enough to penetrate the lattice pattern, may be loosely combined in a neben-valence, or firmly combined in a haupt-valence.

If the cell protein is orientated at the cell surface, the number of chemical combining groups, or free side-chains, is very large. It has been calculated that a small coccus whose volume is 0·25 cubic micra, contains about 2% of nitrogen, which is in turn equivalent to about 12% of protein. If this protein has molecular weight of 36,400—that of egg albumen—then each coccus contains more than 10^6 protein molecules, which is a little more than is necessary to form a mono-molecular layer of protein molecules round the surface of the coccus. It is probable, in the case of the coccus, that the greater proportion of its contained protein is orientated at the cell surface.

Cohn (1925) has calculated that a molecule of egg albumen

contains 27 acid and 27 basic combining groups. The number of protein combining groups or free side-chains per coccus is, therefore, very large; if a proportion of these free side-chains were orientated at the cell surface, they could function, singly or in combination, as areas with which chemical substances could react, and so the internal environment of the cell should be influenced by drugs acting on its surface.

Wrinch (1936), on the other hand, suggests that the protein framework of the cell surface is organized in the following manner. Since proteins consist of optically active combinations of amino acids, she suggests that an hexagonal cyclol structure of laminæ could be orientated, because of the optical activity of the component parts, with all free side-chains on one surface, and that the surface with the free side-chains could function as a template on which complex bio-synthesis could be carried out. The advantage of this theory is the explanation which it offers for the relationship which exists between optical activity and pharmacological action.

These views imply that drugs which act on the surface of living cells react with *free side-chains*, or *specific areas of activity in or on the cell surface* When the fixation of certain powerful drugs —such as the cardiac glucosides, acetyl-choline, adrenaline, etc., which produce a specific action in a very high dilution—is examined, further inference can be made regarding the areas on the cell surface with which these drugs react.

Straub (1910) found that strophanthus gratus produced a lethal effect on isolated frog's heart when a concentration equivalent to about 2 parts of the glucoside per million had been fixed by each gramme of heart tissue. This result is significant because the amount of drug fixed by the heart cells is much less than would be required to cover the surface exposed with a mono-molecular layer of this drug. It is, in fact, sufficient to cover less than 3% of the cell surface with a layer of the drug one molecule thick

Thus: the molecular weight of strophanthus gratus is 760, and 2γ of this drug, therefore, contains 2×10^{15} molecules. One gramme of frog's ventricle contains 3×10^{8} individual cells, and each cell, therefore, fixes $\frac{2 \times 10^{15}}{3 \times 10^{8}} = 10^{7}$ molecules of strophanthus

One molecule of strophanthus covers an area of not less than 500 square Å, and 10^7 molecules, therefore, cover an area of not less than 5×10^9 square Å.

Since the surface area of the cell of a frog's ventricle is 2×10^{11} square Å, it follows that the area of the cell covered by this lethal dose of strophanthus is less than 3% of the total area of the cell surface, for:

$$\frac{5 \times 10^9}{2 \times 10^{11}} \times 100 = 2.5 \text{ per cent. or less than 3 per cent.}$$

In the case of acetylcholine and adrenaline, the amount of drug fixed, when a biological response has been elicited, is an amount which covers only about 0 01% of the cell surface with a layer of drug one molecule thick.

These figures, which have been confirmed by Clark (1933) and others, are, of necessity, only very approximate; but in view of the fact that these drugs are so very specific in their action, it must be inferred that they produce their specific action by uniting with small specified areas of activity in or on the cell surface, and that these specific receptors, or active patches, constitute only a very small proportion of the cell surface. It is probable that any drug, such as a narcotic which produces a specific biological response by acting on the surface of living cells, achieves this end by uniting with particular chemical side-chains, specific receptors, or active patches located in or on the cell surface.

Active Patches. Examples of specific receptors, or active patches, are to be found both in inorganic and organic chemistry. H. S. Taylor (1925) was mainly instrumental in establishing the general recognition of the conception of active patches in inorganic chemistry, and Clark (1933) considered that the phenomenon of active patches in contact catalysis resembled those observed in the case of the specific action of drugs on cells and enzymes far more closely than any other phenomenon in inorganic chemistry.

The activity of a contact catalyst has been shown to depend upon certain isolated atoms, with a high residual field, which constitute a very small proportion of the whole surface of the catalyst. Pease and Stewart (1925) found that 90% of the catalytic activity of a copper surface was due to specific areas which amounted to less than 1% of the whole surface, and Rideal (1926)

states that in the combination of hydrogen and ethylene on a nickel surface, the fraction of the surface which is catalytically active is of the order of 10^{-4}. On this same surface, in addition to the highly refractive areas which adsorbed and caused reaction in these two gases, he found less active areas which adsorbed both gases, but failed to bring them into reaction, and, again, areas which adsorbed ethylene, but not hydrogen.

Thus, several types of active patch are to be found on the same surface of a contact catalyst, each of which exhibits a high degree of specificity in respect to fixation, and the interaction of the chemical groups fixed. This specificity is something more than adsorption displacement, for Pease (1923) found that traces of mercury reduced the adsorptive capacity of a copper surface by 86% for ethylene, and by 20% for hydrogen; but in spite of this reduction of adsorptive power, the catalytic activity of the surface was reduced by less than 1/200 of its original value.

The activity of contact catalysts therefore depends upon *active patches* on the surface of the catalyst; they exhibit a high degree of specificity and constitute a minute fraction of the whole surface area. On the same surface, active patches exist which differ in the character of their reaction and can be inhibited by specific poisons.

Enzymes. In organic life, the reaction of drugs with enzymes illustrates the nature of the active patch, or specific receptor, in a *very simple form of living tissue, and serves to indicate* the importance of protein in pharmacological activity.

Enzymes, antibodies, and compounds such as hæmoglobin and cytochrome, belong to a group of substances which Willstatter and Rhodewald (1934) have called SIMPLEX COMPOUNDS. They consist of an active *prosthetic* group of relatively low molecular weight, attached to a *protein carrier* group of high molecular weight. For example, pure hæmoglobin in watery solution has a molecular weight of 66,000, and each molecule of hæmoglobin contains four ferrous hæm molecules, each with a molecular weight of 630. The compound, therefore, consists of ferrous hæm—the prosthetic group—and native globin—the protein carrier—and the prosthetic group constitutes only about 4% of the hæmoglobin molecule.

The specific activity of these compounds depends upon the action of the prosthetic group with the substrate (the substance to be acted upon). The activity of the prosthetic group appears to depend upon the configuration, or pattern, of its molecules, and it reacts only with chemical substances which fit this pattern. Chemical substances which fit the pattern of the prosthetic group of the simplex compound may serve a useful biological purpose as, for example, the union of oxygen with hæmoglobin; but if, on the other hand, the substance which fits the prosthetic group serves no useful biological function, its combination with the prosthetic group will inactivate the simplex compound. Thus, the union of carbon monoxide with the prosthetic group of hæmoglobin inhibits the biological activity of this compound, cyanide inhibits the activity of the enzyme, indophenol oxidase, and narcotics inhibit the biological activity of the dehydrogenases (Keilin, 1933). The specific nature of the action of enzyme inhibitors uniting with the prosthetic group is indicated by the action of quinine. Thus, quinine inhibits the action of the lipase of serum, pancreas and stomach, but does not affect kidney or liver lipase. Again narcotics exercise a selective inhibition on the dehydrogenases responsible for the oxidation of certain sugars.

The action of enzyme inhibitors which unite with the prosthetic group is freely reversible, as is shown by the immediate return of the functional activity of hæmoglobin and dehydrogenases, after the dissociation of carbon monoxide and narcotics respectively, from the prosthetic group of these simplex compounds.

Simplex compounds may also be inactivated in an irreversible manner by the denaturation of the protein carrier by non-specific agents, such as drugs, heat, ultra-violet light, strong acids, strong alkalis, etc.; moreover, the functional activity of the prosthetic group is dependent upon the functional activity of the protein carrier. When, for example, the protein carrier of hæmoglobin—native globin—is denatured, the iron of the prosthetic group is oxidised to the ferric state on exposure to oxygen. The compound then becomes ferric hæm and denatured globin, and the oxygen-carrying capacity of the compound is lost permanently, for ferric hæm is an irreversible substance.

Jacoby (1933) found that the inhibition of the enzyme, urease

by copper was at first reversible, but later became irreversible. He found that the initial combination of copper with the prosthetic group produced a reversible inhibition, and that this was followed by a slow denaturation of the protein carrier by the copper, which was irreversible. This type of action is probably responsible for the coagulation of protein which occurs with high concentrations of phenol and chloroform.

The normal biological activity of simplex compounds therefore depends upon the ability of the normal biological substrate to unite with the prosthetic group of the compound, and the prosthetic group may be looked upon as the *active patch*, or *specific receptor*, of this simple form of living tissue. Enzyme inhibitors unite with the prosthetic group of the enzyme to the exclusion of the normal biological substrate. Their specificity depends upon the possession of chemical radicals or groups in the molecule of the drug, enabling it to unite with specific radicals in the molecular constitution of the active patch or prosthetic group of the enzyme.

Narcotics act specifically on a number of enzymes in a reversible manner, and the specificity and reversibility of their action suggests that narcotics inhibit the action of these enzymes by *uniting with the prosthetic group to the exclusion of the normal biological substrate* In contradistinction, non-specific enzyme poisons produce their action by the denaturation of the protein carrier of the enzyme, and their action is not reversible because the protein carrier is necessary for the functional activity of this form of life.

The following is the probable chain of events when a narcotic in an effective concentration is brought into contact with an enzyme (1) uptake of the narcotic by the enzyme, by means of a water solubility mechanism or by an adsorption process, depends on the physical properties of the particular narcotic: (2) there follows, when a certain critical concentration has been reached, the *adsorption displacement* of the normal biological substrate from the prosthetic group, and the fixation of the narcotic to the prosthetic group, with consequent inhibition of the normal function of the enzyme.

Cells. The presence of active patches, or specific receptors, in or on the surface of living cells is suggested by the observations

already quoted of the action of certain potent specific drugs which act in high dilution. It seems probable that when a drug produces a specific response by surface action this biological response is

TABLE 7 (QUASTEL & WHEATLEY, 1932).

Inhibitive Action of Gaseous Narcotics			
	N_2/air = 3/1	N_2O/air = 3/1	INHIBITION
O_2 uptake in c.mm. by tissue alone	219	250	0%
Extra O_2 uptake in presence of glucose (0.05%)	265	190	28%
	N_2/air = 1/1	C_2H_2/air = 1/1	Inhibition
O_2 uptake by tissue alone	160	162	0%
Extra O_2 uptake in presence of glucose (0.05%)	225	152	33%
	Air	Air/Ether Vapour	Inhibition
O_2 uptake by tissue alone	340	158	53%
Extra O_2 uptake in presence of glucose (0 05%) . .	350	173	51%

produced by the fixation of the drug to areas of specific activity situated in or on the cell membrane. Quastel (1930) has shown that the ferment action of certain bacteria was due to patches of activity on the bacterial cell membrane; by means of selective dyes he was able to identify twelve different varieties of active patch on the surface of B Coli.

Quastel and Wheatley (1933), using di-alkyl-barbituric acid derivatives, whose physical properties are such that they may

be compared quantitatively, showed that a marked parallelism existed between the narcotic activity of a drug and its ability to inhibit the oxidation of fresh brain tissue. The same result was observed with muscle, kidney and liver tissue, but the intensity of inhibition was less with these tissues than with brain, and the results with liver tissue were not constant. They showed, moreover, that this relationship obtained with narcotics of dissimilar chemical constitution, such as hyoscine, morphia, chloral hydrate, luminal and cocaine. When the gaseous anæsthetics were compared, Table 7 showed that ether vapour depressed the oxidations of fresh brain tissue by 53%, but nitrous oxide and acetylene produced no such inhibition, and could be considered weak narcotics.

Henderson (1930), however, asserts that "no theory of anæsthesia will prove acceptable which is based on a proof of a depression of the resting metabolism of the cell. . . . The facts distinctly show that oxidative processes and narcosis are separate phenomenon."

If this reduction of cell oxidation produced by narcotics is represented as a generalized diminution of all the oxidative processes of the cell, then Henderson is correct in his first assertion, for, in this case, the biological action of oxygen lack and narcotics would be identical. But narcotics do not interfere with the access of oxygen to living cells, or the uptake of oxygen by cells; the various asphyxiation theories *have failed completely* to explain many of the facts connected with narcosis, and are at variance with the fact that narcosis may be produced in cells which lead an anærobic existence.

The resting oxidations of a cell consist, however, of numerous metabolic processes, and, in normal conditions of life, the interrelation between the activity of these many oxidative processes is not constant but responds to varying environmental and biological changes. A diminution of the oxidation of the cell as a whole, therefore, is not *per se*, an indication of the magnitude or the nature of the particular metabolic process or processes which are responsible for this diminution in oxidation. Since narcotics do in fact diminish the oxidation of the cell, the problem resolves itself

into one of rationalizing the facts at our disposal, as *a selective inhibition of a particular form of metabolic activity which must apply alike to ærobic and anærobic forms of life.*

It must be borne in mind that oxidation consists of the addition of oxygen or the removal of hydrogen from the substrate, and on the hypothesis that a substrate may undergo oxidation by the simple loss of hydrogen, it is clear that this form of oxidation may apply to both ærobic and anærobic forms of life. On the one hand the activated hydrogen is passed to a hydrogen acceptor, which under ærobic conditions may be molecular oxygen obtained from oxidised cytochrome. On the other hand, the activated hydrogen is passed, under anærobic conditions, to a hydrogen acceptor which may be any substance which is readily reduced. In both ærobic and anærobic forms of life, therefore, the inhibition of the enzymes, dehydrogenases, which are the hydrogen activators of this form of cell oxidation, would result in the inability of the cell to metabolise this form of substrate—not, as has been suggested, because oxidised cytochrome cannot be reduced—but, on the contrary, because the dys-oxidisable substrate cannot be activated.

There are many substances of physiological importance, such as glucose, which do not unite readily with molecular oxygen at body temperature, and they are called dys-oxidisable substances. Keilin (1925) showed that narcotics produce their specific biological action on cells by inhibiting the activity of the enzymes, dehydrogenases, which are the hydrogen activators of these dys-oxidisable metabolites. Davis and Quastel (1932) found that the dehydrogenation of glucose, lactate and pyruvate was greatly inhibited by narcotics but that the oxidation of succinate and certain other metabolites was not greatly affected. Quastel and Wheatley (1933) observed that the inhibition of brain oxidation by narcotics was a selective inhibition; Table 8 taken from their work shows that narcotics which differ in their molecular constitution inhibit equally and in a powerful manner, the brain oxidation of the substrates *glucose, sodium lactate* and *sodium pyruvate.* Sodium glutamate was inhibited to a lesser degree but the oxidation of sodium succinate and phenylenediamine was in no way affected. Reference to Table 7 shows that the gaseous anæsthetics,

TABLE 8 (QUASTEL AND WHEATLEY .

Percentage Inhibition by Narcotics
of
Extra Oxygen Uptake Due to Various Substrates.

NARCOTIC (0 12%)	GLUCOSE 0 0015 M	SODIUM LACTATE 0 0125 M	SODIUM PYRUVATE 0 0125 M	SODIUM SUCCINATE 0·05 M	SODIUM GLUTAMATE 0·05 M	PHENYLENE -DIAMENE 0 05 M
Allyliso barbituric ac.	73	71	67	2	28	0
Phenylethyl barbituric ac	94	79	85	0	50	0
Diethyl barbituric ac	20	22	29	0	0	0
Ethyl urethane	17	16	12	0	13	—
Chloretone	93	88	84	0	59	—
Hyoscine	79	73	71	0	60	—
Chloral hydrate	66	90	90	0	62	—
Paraldehyde	3	0	2	0	32	—
Morphia	32	30	30	0	24	—

which have not been investigated so thoroughly, inhibit the oxidation of the dys-oxidisable metabolite, glucose.

There can be little doubt that diminution of cell oxidation produced by narcotics results from the selective inhibition of the oxidation of glucose, lactate, pyruvate and glutamate while succinate metabolism and the uptake of molecular oxygen is unaffected. It is known that narcotics inhibit the action of the dehydrogenases of glucose, lactate and pyruvate and that they do not inhibit the action of succinate dehydrogenase or cytochrome oxidase. Moreover, in a study of the inhibitory action of chloretone on the lactic acid dehydrogenase of minced brain tissue under anærobic conditions Davies and Quastel (1932) found that the narcotic competed with the substrate (sodium lactate) for the dehydrogenase, according to the law of mass action. The simplest explanation of the diminution of cell oxidation by narcotics is therefore the selective inhibition of the specific dehydrogenases responsible for the brain oxidation of glucose, lactate and pyruvate, produced by the absorption displacement of the normal substrate from the prosthetic group of these enzymes by the narcotic. In this instance too, succinate oxidation continues unimpeded and the uptake of molecular oxygen by cell cytochrome is unaffected.

Warburg, Quastel and others have shown that respiratory enzymes do occur in or on the cell membrane. Since narcotics produce their characteristic biological response on the cell surface and not in the cell interior, it is probable that the specific dehydrogenases inhibited by narcotics are located in or on the cell membrane. If the protein carrier of these specific simplex compounds formed part of the protein constituent of the cell membrane, with its prosthetic group orientated towards the surface of the cell, this arrangement would permit narcotics adsorbed to or dissolved in the cell membrane to unite with the prosthetic group and thus inhibit in a freely reversible manner the biological function of these specific dehydrogenases. In this instance, the prosthetic group of these specific dehydrogenases, located in or on the cell membrane, would constitute the active patch or specific receptor to which narcotics fix themselves. This mechanism of the selective inhibition of these dys-oxidisable metabolites could apply alike to ærobic and anærobic forms of life.

This simple explanation of the selective inhibition of the carbohydrate metabolism of the brain by narcotics at biologically important concentrations which has been generally accepted in the past, is no longer adequate. Quastel (1950) has produced further evidence which indicates that the site of action of narcotics on the

TABLE 9.

THE EFFECT OF SUBSTRATE CONCENTRATION ON THE INHIBITION OF BRAIN CORTEX RESPIRATION (Qo_2) BY NARCOTICS (QUASTEL, 1950)

Animal	Substrate	Narcotic	% Inhibition of Qo_2
Rat	Na Pyruvate 0·08 M.	Chloretone 0 037%	37
	Na Pyruvate 0 01 M	Chloretone 0 037%	37
Guinea-pig	Na Pyruvate 0 06 M.	Luminal 0 08 %	27
	Na Pyruvate 0 01 M.	Luminal 0 08 %	28
Guinea-pig	Na d Lactate 0 06 M	Luminal 0 08 %	39
	Na d Lactate 0 01 M	Luminal 0 08 %	31

carbohydrate metabolism of the brain is not the dehydrogenases but a more narcotically sensitive component in the chain of events midway between dehydrogenases and cytochrome oxidase. Quastel's data and argument in support of this thesis are outlined below.

Reference to Table 9 shows that chloretone and luminal inhibit the oxidation of lactate and pyruvate by the brain cortex but it also shows that an increase in the concentration of the substrate (lactate or pyruvate) does not diminish the intensity of the inhibition of oxidation produced by a constant concentration of the narcotics If competition between these narcotics and the lactate or pyruvate for the prosthetic group of the dehydrogenases was the factor acting, then a sufficient increase in the concentration of the substrate should diminish or abolish the inhibition of the oxidation of these substrates produced by these narcotics. This in fact does not occur and this observation suggests that the dehydrogenases are not the link in the chain of carbohydrate metabolism acted on by narcotics.

The observations of Overton (1901), Winterstein (1913), Veszi (1918) and others show that anærobic protozoa require a greater concentration of a narcotic to depress them than is the case with ærobic forms of life and Quastel (1950) points out that low

TABLE 10.

THE EFFECT OF CHLORETONE ON ANÆROBIC GLYCOLYSIS BY THE BRAIN (MICHAELIS AND QUASTEL, 1941).

Rat brain cortex slices in sodium bicarbonate (0 025 M)-Locke solution containing 0 025 M glucose and 0 003 M sodium pyruvate; 95% nitrogen and 5% of carbon dioxide, at 37°C.

		$Q_M^{N_2}$		
Medium without chloretone		15 2	19 8	16 5
Medium with chloretone	0 033%	15 1	—	—
Medium with chloretone	0 05 %	—	17·8	16 4

concentrations of narcotics which inhibit brain oxidation in a powerful manner under ærobic conditions, have little or no inhibitory action on brain oxidation under anærobic conditions. Thus, under ærobic conditions, chloretone (0·016%) produces a 50% inhibition of the respiration of brain suspensions or slices in the presence of lactate but Michaelis and Quastel (1941) observed when lactate was oxidised by brain tissue anærobically, using ferricyanide as the terminal hydrogen acceptor, that chloretone even at a concentration of 0 083% produced no inhibition of respiration. If the lactate dehydrogenase mechanism which is responsible for the reduction of ferricyanide under anærobic conditions is the same as that which activates lactate under ærobic conditions, this result infers that the latter cannot be the narcotic sensitive component of the ærobic respiratory mechanism. Again, Table 10 shows the complete absence of any inhibition of oxidation when brain slices in the presence of glucose and sodium pyruvate are subjected anærobically to the action of chloretone in concentrations up to 0 05%. The dehydrogenases which are responsible for the anærobic oxidation of glucose in the brain, are also concerned in the ærobic breakdown of glucose in the brain. Hence, the absence of the narcotic depression of glucose oxidation by the brain under anærobic conditions indicates that if a narcotic sensitive dehydrogenase system plays a part in the ærobic breakdown of glucose, it is either absent or is without influence in, the reactions concerned with the anærobic breakdown of glucose by the brain.

These several data led Quastel to infer that narcotics in a low concentration exert their dominant action under ærobic conditions, not on dehydrogenases but on a part of the mechanism of the oxidation of these sugars that is inert or functionless under anærobic conditions. He postulates that this respiratory entity has the properties of an enzyme structure, for it is affected in a freely reversible manner by the surface action of so many different types of narcotics and that it must be a tissue constituent with a much higher affinity for narcotics than the most sensitive enzymes (the dehydrogenases) with which we are so far familiar.

TABLE 11.

GLUCOSE DEHYDROGENASE (ACETONE PIG LIVER) PREPARATION (MICHEALIS AND QUASTEL, 1941).

1. 1 ml. glucose dehydrogenase preparation, 1 mg. cozymase preparation; 0 025 M Na bicarbonate saline; glucose 0 016 M; 0 2 ml. 8 3% Pot. ferricyanide solution added; 95% nitrogen and 5% carbon dioxide; 37°C

	μ l. CO_2 output in 60 minutes.
Glucose dehydrogenase	88 9
Glucose dehydrogenase + cozymase	96 0
Glucose dehydrogenase + glucose	68 5
Glucose dehydrogenase + cozymase + glucose	233 3

2. 1 ml. glucose dehydrogenase preparation; 1 mg. cozymase preparation, 0 025 M Na bicarbonate saline, glucose 0 1 M; 0·2 ml 8 3% Pot. ferricyanide solution added, 95% nitrogen and 5% carbon dioxide; at 37°C.

	μ l. CO_2 output in 30 minutes.
Glucose dehydrogenase + cozymase	75·4
Glucose dehydrogenase + cozymase + chloretone (0 083%)	75 6
Glucose dehydrogenase + cozymase + glucose	325 8
Glucose dehydrogenase + cozymase + glucose + chloretone (0 083%)	329 7
Inhibition by chloretone	2%

Table 11 shows when glucose in the presence of a water soluble preparation of glucose dehydrogenase is oxidised anærobically by ferricyanide in the presence of cozymase, that chloretone (0 083%) fails to inhibit the oxidation of glucose. If, however, a crude preparation of cytochrome oxidase is added to the dehydrogenase-cozymase system so that added glucose is oxidised ærobically, it is seen in Table 12 that this system immediately becomes

susceptible to the action of narcotics and chloretone (0 083%) inhibits the oxidation of glucose by 90%.

TABLE 12.

GLUCOSE DEHYDROGENASE (ACETONE PIG LIVER) PREPARATION AND CYTOCHROME OXIDASE (PIG HEART) PREPARATION (MICHAELIS AND QUASTEL, 1941).

1. 1 ml. glucose dehydrogenase preparation; 0·25 g in 8 ml. cytochrome oxidase preparation; 1 mg. cozymase preparation in Na phosphate (0·03 M); pH 7 4 saline; glucose 0 016 M; air; at 37°C.

	μ 1. of oxygen in 60 minutes.
Glucose dehydrogenase + cozymase + glucose	0 0
Glucose dehydrogenase + cytochrome oxidase + glucose	6·0
Glucose dehydrogenase + cytochrome oxidase + cozymase	5·0
Glucose dehydrogenase + cytochrome oxidase + cozymase + glucose	80.6
2. Glucose dehydrogenase (1 ml. of solution of 0·5 g. in 8ml. saline) + cytochrome oxidase + cozymase + glucose (0 1 M)	341·2
Glucose dehydrogenase + cytochrome oxidase + cozymase + glucose + chloretone (0 083%)	8·4
Inhibition by chloretone	97%

It can be concluded that the dehydrogenases responsible for the oxidation of glucose, lactate and pyruvate are relatively insensitive to narcotics and that the diminution of the oxidation of these substrates by narcotics under ærobic conditions depends upon the inhibition of a narcotically sensitive intermediate factor in the chain of events, somewhere between dehydrogenase and cytochrome oxidase. In the oxidation of lactate in animal tissues, this intermediate factor must take part in the reactions between reduced cozymase and one of the cytochromes. In the experiment shown in Table 12, flavoprotein with cytochrome compounds was present in the crude cytochrome oxidase preparation used, and Quastel believes that flavoprotein plays an important part in the ærobic oxidation of these sugars. Greig (1946) considers that in the presence of narcotics there is a binding of reduced flavoprotein with cytochrome b or some other intermediate. This intermediate factor must be absent in the ærobic oxidation of succinate in animal tissues, for succinate oxidation is not inhibited by narcotics. It seems probable that narcotics reach a mass action equilibrium with a special entity in the chain of ærobic oxidation of glucose,

These several data led Quastel to infer that narcotics in a low concentration exert their dominant action under ærobic conditions, not on dehydrogenases but on a part of the mechanism of the oxidation of these sugars that is inert or functionless under anærobic conditions. He postulates that this respiratory entity has the properties of an enzyme structure, for it is affected in a freely reversible manner by the surface action of so many different types of narcotics and that it must be a tissue constituent with a much higher affinity for narcotics than the most sensitive enzymes (the dehydrogenases) with which we are so far familiar.

TABLE 11.

GLUCOSE DEHYDROGENASE (ACETONE PIG LIVER) PREPARATION (MICHEALIS AND QUASTEL, 1941).

1. 1 ml glucose dehydrogenase preparation, 1 mg. cozymase preparation; 0 025 M Na bicarbonate saline; glucose 0 016 M; 0·2 ml. 8 3% Pot. ferricyanide solution added; 95% nitrogen and 5% carbon dioxide; 37°C

	μ 1. CO_2 output in 60 minutes.
Glucose dehydrogenase	88.9
Glucose dehydrogenase + cozymase	96·0
Glucose dehydrogenase + glucose	68 5
Glucose dehydrogenase + cozymase + glucose	233 3

2 1 ml. glucose dehydrogenase preparation; 1 mg cozymase preparation; 0 025 M Na bicarbonate saline, glucose 0 1 M, 0 2 ml. 8 3% Pot. ferricyanide solution added, 95% nitrogen and 5% carbon dioxide; at 37°C

	μ 1. CO_2 output in 30 minutes.
Glucose dehydrogenase + cozymase	75·4
Glucose dehydrogenase + cozymase + chloretone (0 083%)	75 6
Glucose dehydrogenase + cozymase + glucose	325 8
Glucose dehydrogenase + cozymase + glucose + chloretone (0 083%)	329 7
Inhibition by chloretone	2%

Table 11 shows when glucose in the presence of a water soluble preparation of glucose dehydrogenase is oxidised anærobically by ferricyanide in the presence of cozymase, that chloretone (0 083%) fails to inhibit the oxidation of glucose. If, however, a crude preparation of cytochrome oxidase is added to the dehydrogenase-cozymase system so that added glucose is oxidised ærobically, it is seen in Table 12 that this system immediately becomes

and they do not interfere with the uptake of oxygen and the activation of cell cytochrome or with the uptake and activation of molecular oxygen by cell metabolites.

Himwich and Nahum (1929) concluded that carbohydrate was used exclusively by the brain as a source of energy and even in diabetes mellitus the utilization of carbohydrates by the brain seemed unimpaired.

Quastel and Wheatley therefore suggest that the inhibition of the oxidation of glucose, and pyruvic and lactic acids diminishes the energy available for the cell to accomplish its normal functional activity and so produces a state of narcosis. Narcotics also inhibit the oxidation of the sugar-forming amino acid, glutamic acid, and this appears to be an effort to exclude an additional form of carbohydrate-produced energy and to restrict the carbohydrate energy of the cell to that supplied by the oxidation of succinic acid which, it is assumed, is the minimal amount of carbohydrate energy compatible with the continued life of the cell. They also drew attention to the " saving action " of this succinate carbohydrate metabolism during narcosis and they assert that succinate metabolism during narcosis ensures that narcotics can have no injurious effect on the oxidations of the brain as a whole or on the ability of the brain cells to activate molecular oxygen. It is concluded, on this account as also because of the specific nature of narcotic depression, that narcotics cannot be considered as " tissue poisons " in the accepted meaning of the term.

It is impossible to escape the suggestion that the state of narcosis must be attributed to the diminution of cell energy which results from the inhibition of the oxidation of glucose, lactate and pyruvate This supposition can be co-related with the diminished synthesis of acetylcholine which occurs during narcosis and is discussed in Chapter 23.

REFERENCES.

1 BOTZER, E, and COLE, K S (1935). *J cell comp Physiol.* 6, 229.
2 BRINDLEY, F J (1928). *Proc Soc exp Biol N Y.* 25, 305.
(1928) *J gen Physiol* 12, 201.
3. CHAMBERS, R (1926) " Harvey Lectures " (Harvey Soc. N.Y.) 22, 41.
4 CLARK, A. J. (1933) "The Mode of Action of Drugs on Cells," p. 17, Edward Arnold & Co, London
5 COWLES, G. H A. (1916). *J. phys Chem.* 20, 407.
6. DANIELLI, J F., and DAVSON, H (1934) *J cell comp Physiol* 5, 495
7 DANIELLI, J. F, and HARVEY, E N (1934). *J. cell comp. Physiol.* 5, 483.
8 DAVIS, D. R., and QUASTEL, J. H. (1932). *Biochem. J.* 26, 1672.

lactate and pyruvate, which has an intermediate role between cozymase and cytochrome. Quastel's scheme of the probable site of action of narcotics is shown in Table 13.

TABLE 13.

NARCOTIC-SENSITIVE RESPIRATORY SYSTEM (QUASTEL, 1950).

Substrate→Dehydrogenase→Cozymase→Flavoprotein→Cytochrome→Cytochrome oxida →Oxygen

Narcotic Insensitive Region	Narcotic Sensitive Region	Narcotic Insensitiv Region

The evidence set out above and the conclusions drawn from this data are a version of the manner in which narcotics act on living cells and enzymes, but not an explanation of why this chain of events should be followed by the characteristic depression of the functional activity of living cells, which we know as narcosis.

In therapeutic doses, narcotics do not interfere with the uptake and the activation of oxygen by living cells. This is in marked contrast to the action of potassium cyanide which, by inhibiting the enzyme, indophenol oxidase, prevents the uptake of oxygen by cell cytochrome and it therefore prevents the oxidation of oxygen acceptors—even oxygen acceptors as freely oxidisable as succinic acid. On the other hand, narcotics, in concentrations of such an order as to produce deep anæsthesia in animals, inhibit equally and in a powerful manner the oxidation of glucose, pyruvic acid and lactic acid, which are metabolites of great importance in the carbohydrate metabolism of brain cells. At this same concentration, narcotics do not inhibit the oxidation of succinic acid, which is also an intermediate product of carbohydrate metabolism Iodo-acetic acid, on the contrary, inhibits the oxidation of glucose but does not affect the oxidation of pyruvic and lactic acids to the same degree, and this substance is not a narcotic.

It therefore appears that the distinctive properties of narcotics are three-fold: they inhibit the intracellular oxidation of pyruvic and lactic acid as powerfully as they inhibit the oxidation of glucose; they do not inhibit the oxidation of succinate acid;

CHAPTER VI

DISCUSSION

NARCOTICS exert a graded action on living cells and the intensity of narcosis varies sometimes directly and sometimes in a logarithmic manner, as the concentration of the narcotic in the extracellular fluid in contact with living cells.

In its simplest form, the chain of events resulting in a state of narcosis consists of the uptake of the narcotic by the cell, followed by its fixation by the cell; this in turn is followed by the specific response of the cell, which is termed narcosis.

Evidence has been examined which indicates that the uptake of narcotics by living cells is a differential solubility process and when narcotic equilibrium has been assumed in the narcotic-cell system, the absorptive capacity of the cell for the narcotic varies in keeping with the physical properties of the narcotic, sometimes directly and sometimes in logarithmic manner, as the concentration of the narcotic in the extracellular fluid in contact with the living cell.

A direct relationship is observed between concentration and action in narcotics of relatively low molecular weight and potency such as di-ethyl ether, whose uptake by living cells is directly proportional to its concentration in extracellular fluid In the case of narcotics of high molecular weight and potency which act in a high dilution, such as morphia, a logarithmic relationship exists between concentration and action, and it has been observed that the uptake of such narcotics by living cells is proportional to the logarithm of their concentration in extracellular fluid. There is reason to believe that it is the physical properties of a narcotic which determine the method of its uptake and in turn the direct or logarithmic character of its action on living cells. In each instance it can be inferred that the fixation of the narcotic is proportional to its concentration at the site of drug fixation in the cell, and that the intensity of narcotic action is proportional to the mass of narcotic fixed by the cell. The ability to attain

9. GREIG, M. E. (1946). *J. Phar. exp. Therap.* 87, 185.
10. HENDERSON, V. E. (1930). *Physiol Rev.* 10, 171.
11. HEILBRUNN, L. V. (1936). *Biol Bull.* "Wood's Hole." 71, 299.
12. HILL, A. V., and KUPALOV, P. S. (1930). *Proc roy. Soc. B.* 106, 445.
13. HILLER, S. (1927). *Proc. Soc. exp. Biol. N.Y.* 24, 427, 938.
14. HIMWITCH, H. E., and NAHUM, L. H. (1929) *Amer. J. Physiol.* 90, 389.
15. JACOBY, M (1933) *Biochem. Z.* 262, 181.
16. KEILIN, D (1925) *Proc roy Soc. B.* 98, 312.
17. MARSLAND, D. (1934) *J. cell. comp. Physiol.* 4, 9.
18. MICHEALIS, M., and QUASTEL, J. H (1941). *Biochem. J.* 35, 518.
19. OVERTON, E. (1901) *Studien uber die Narkose. Jena.*
20. PEASE, R. N. (1923). *J. Amer. chem. Soc.* 45, 1196, 2235, 2296.
21. PEASE, R. N., and STEWART, L. (1925). *J. Amer. chem. Soc.* 47, 1235.
22. QUASTEL, J. H (1930) *Trans Faraday Soc.* 26, 853.
23. QUASTEL, J. H (1950) Read before the International Conference on Narcosis, Paris Personal communication.
24. QUASTEL, J H, and WHEATLEY, A. H. M (1932). *Proc. roy. Soc. B.* 112, 60.
25. REZNIKOFF, P. (1926). *Proc. Soc. Biol., N.Y.* 24, 380.
26. RIDEAL, E K (1926). "An Introduction to Surface Chemistry." p. 141 Cambridge University Press.
27. RIDEAL, E K (1937) *Trans Faraday Soc.* 33.
28. ROUGHTON, F J W. (1934) *Proc roy. Soc. B.* 115, 451, 464.
29. STRAUB, W (1910) *Biochem. Z.* 28, 392.
30. TAYLOR, H S. (1925). *Proc. roy Soc A.* 108, 105
31. VESZI, J. (1918) *Pflug. Arch ges Physiol* 170, 313
32. WILLSTATTER, R, and RHODEWALD, M (1934) *Hoppe-seyl Z.* 225, 103
33. WINTERSTEIN, H. (1913) *Biochem. Z.* 51, 143.
34. WRINCH, D M (1936). "Nature," Lond. 138, 651.

part which carbohydrate metabolism plays in its normal functional activity, and this in turn implies that each and every type of living cell possesses a characteristic number of specific narcotic receptors.

It has been observed, when the concentration of a narcotic in extracellular fluid is sufficient to produce maximum narcotic action on a particular type of living cell, that a further increase in the concentration of the narcotic in extracellular fluid fails to produce additional narcotic action. This inability to increase the intensity of narcosis beyond a certain degree cannot be due to an arrest of the uptake of the narcotic by the cell, for when the concentration of the narcotic in extracellular fluid is increased beyond what is required to produce maximum action, a concentration of the narcotic is at length achieved which produces an irreversible coagulation of cell protoplasm; the cell then dies. This indicates that the critical precipitation concentration of the narcotic has been achieved in the cell interior. If however the particular type of living cell possesses a characteristic number of specific narcotic receptors, it follows that, when the concentration of the narcotic in extracellular fluid is sufficient to produce narcotic fixation in each and every narcotic receptor, maximum fixation and in turn maximum action are achieved. In this instance the saving action of succinate metabolism ensures that the state of narcosis is freely reversible. There is reason to believe that each and every type of living cell possesses a characteristic number of specific narcotic receptors, which may explain the individual susceptibility which different types of living cell exhibit to narcotics.

narcotic fixation depends upon the presence of specific combining groups in the molecule of the narcotic. Hence, the chemical constitution of the drug determines that it can attain narcotic fixation and produce narcosis and its physical properties determine the character of uptake and fixation, the mass of narcotic fixed, and in turn the character and intensity of the action produced by a given concentration of the narcotic in extracellular fluid.

Narcotics act in or on the cell surface of living cells and evidence has been discussed which suggests that they are fixed by specific narcotic receptors located in or on the cell surface. It is probable that the narcotic receptors of living cells consist of the prosthetic group of a co-enzyme midway between cozymase and cytochrome in the chain of oxidation of the dys-oxidisable metabolites, glucose, lactic acid, pyruvic acid and glutamic acid.

The data examined suggests that narcotics displace the normal biological substrate from the prosthetic group of these enzymes by an adsorption displacement mechanism. In this instance, a certain critical concentration of the narcotic must be achieved at the site of drug fixation in the cell before the normal substrate is displaced and its place taken by the narcotic; this would explain the fact that there is a certain minimal threshold concentration below which a particular narcotic fails to produce its characteristic response on a given type of living cell. If moreover these narcotic receptors were located in or on the cell surface, this in turn would account for the rapid response produced, not only by narcotics which readily penetrate the cell surface, but also by narcotics to which the cell surface is relatively impermeable. In the case of relatively impermeable narcotics, receptors located in or on the cell surface would account for the fact that maximum biological response can occur with these narcotics, before the cell is saturated with the narcotic

Specific receptors of this nature also explain why narcotics act in a characteristic fashion not only on ærobic but also on anærobic forms of living tissue, and they rationalize the specific nature of narcosis, while the saving action of succinate metabolism offers an explanation of the freely reversible nature of narcosis.

It is moreover probable that each and every type of living cell has a characteristic number of such enzymes in keeping with the

PART TWO

ANAESTHETICS

PART TWO

ANAESTHETICS

CHAPTER VII

1. INTRODUCTION

WHEN a narcotic in an effective concentration is brought into contact with any one of the many types of cells which comprise the body of a heterogeneous cell system such as Man, these cells are depressed in a graded manner and the intensity of narcotic depression varies as the concentration of the narcotic at the site of its drug fixation in the living cell.

An anæsthetic is a narcotic drug that can be employed in a controllable manner in clinical practice; the problem of determining the mode of action of anæsthetics in Man is that of deciding:

1. How an anæsthetic is concentrated in an effective solution at the site of narcotic fixation in the cells of Man's body.
2. Why, generally speaking, non-nervous cells escape the action of anæsthetics
3. How the selective action of anæsthetics on nervous cells can be controlled.

The full problem can be answered when we understand the mode of uptake of anæsthetics by the cells of a Man's body, for, after uptake has been effected, fixation and then action must follow.

In clinical practice, anæsthetics are brought into contact with the cells of a heterogeneous cell system such as Man in two ways. Firstly, the anæsthetic may be dissolved in circulating blood and so carried to the capillaries of its various organs, to diffuse from thence, *via* extracellular fluid to the cells themselves. Irrespective of the method adopted to dissolve anæsthetics in circulating blood, all blood-borne anæsthetics exert a dominant pharmacological action on the cells of the central nervous system; they are consequently often called general anæsthetics. Secondly, anæsthetics may be applied directly to mucous membranes or injected directly into the vicinity of the peripheral nerves to diffuse *via* extracellular fluid to the nerves themselves. In this instance, they exert a

of the central nervous system to local anæsthetics carried to it in an effective concentration by circulating blood is a distorted version of the standard safe sequence of response.

To be suitable for use in clinical practice as a blood-borne anæsthetic, a narcotic must depress the cells of the body in the standard sequence, and a local anæsthetic must depress nerve endings and peripheral nerves without at the same time producing depression of the central nervous system; and in each instance it must be possible to concentrate the narcotic at the site of its drug fixation in a controllable manner.

The concentration of a blood-borne anæsthetic in the cells of the central nervous system and, in turn, the level of anæsthetic depression produced, are determined primarily by the concentration of the anæsthetic in circulating blood; and this depends not only on the mass of anæsthetic dissolved in circulating blood per unit time, but also on the mass of anæsthetic cleared from circulating blood per unit time. The control of the blood concentration of a particular blood-borne anæsthetic must be discussed in terms of the *uptake* of the anæsthetic by circulating blood and its *excretion* from it.

The methods adopted in clinical practice to dissolve blood-borne anæsthetics in circulating blood—that is, their "*method of approach*" to circulating blood—permit the members of this group to be divided into four sub-groups, which are:

1. Inhalation anæsthetics.
2. Intravenous anæsthetics.
3. Oral and Rectal anæsthetics.
4. Subcutaneous and Intramuscular anæsthetics.

In clinical practice, the method of approach of a blood-borne anæsthetic to circulating blood is determined mainly by the physical properties of the particular anæsthetic. Volatile anæsthetics—the anæsthetic gases and vapours—are most conveniently dissolved in circulating blood through the medium of the respiratory system. Non-volatile blood-borne anæsthetics—liquid and solid—cannot be dissolved in circulating blood through the medium of the respiratory system. An alternative method of approach, suitable to the physical properties of the particular anæsthetic,

dominant pharmacological action on nerve endings or peripheral nerves; narcotics used in this fashion are called local anæsthetics.

Anæsthetics thus fall naturally into two distinct groups, viz.:

Blood-borne Anæsthetics and Local Anæsthetics

When dissolved in circulating blood in an effective concentration, narcotics suitable for use in clinical practice as blood-borne anæsthetics not only selectively depress the cells of the brain: they depress the cells of this organ in such a manner that consciousness is lost first, then the ability to react to external stimulus, then muscle tone in all striated muscles except the diaphragm is abolished and finally the vital medullary centres are depressed, in the order: respiratory centre, the vasomotor centre and, as an end result, the cardiac centre. This sequence of depression of the various levels of functional activity of the central nervous system—clearly a thoroughly safe sequence—will be referred to in this discussion as the "*Standard sequence of the response of the body to blood-borne anæsthetics.*" Although local anæsthetics and certain other narcotics, such as chloroform and ethyl alcohol, depress the cells of the central nervous system when dissolved in circulating blood in an effective concentration, they may not depress the body in the above standard sequence: the heart or the vital medullary centres (or both) may be depressed even before or soon after consciousness is lost. This distortion of the standard sequence of the biological response of the body to local anæsthetics (and to certain other narcotics to be discussed later) renders them dangerous drugs when used as blood-borne anæsthetics in clinical practice.

Narcotics suitable for use in clinical practice as local anæsthetics depress the functional activity of nerve endings and peripheral nerves in a characteristic fashion when effectively concentrated in these cells. But the concentration of the narcotic required at the site of application or injection to achieve this end is such that the mass of narcotic absorbed from the site of injection into circulating blood *produces a blood concentration which is below the minimum threshold concentration of the narcotic necessary to depress the cells of the central nervous system.* And it is clear that a local anæsthetic that cannot produce an effective anæsthetic preparation locally, without at the same time depressing the cells of the central nervous system, is a dangerous drug, for the response

excretion is largely instrumental in determining the safest method of approach to circulating blood and the field of their clinical usefulness. Because of the slow and inflexible character of their excretion, non-volatile non-reactive anæsthetics such as barbitone are usually administered by mouth in hypnotic doses.

Reactive non-volatile anæsthetics, such as evipan and pentothal, are detoxicated by the liver prior to the excretion of their harmless degradation products in the urine by the kidneys. In health, this form of excretion may be almost as rapid as that of volatile anæsthetics by the lungs. The rate of excretion of reactive non-volatile anæsthetics cannot however be hastened in any way; but when liver inefficiency is present, or when circulatory failure reduces the minute blood-flow through the liver, excretion may be slowed to a dangerously low rate. In health, the rapidity of excretion permits the concentration of these anæsthetics in circulating blood to be varied in an upward and a downward direction by alteration in the rate of uptake, in a manner comparable to, but not so rapid and as flexible as, that of volatile anæsthetics; and they may be administered intravenously in clinical practice for the production of surgical anæsthesia.

Finally there is a group of non-volatile anæsthetics which are excreted, in part after detoxication by the liver and in part unchanged, by the lungs and/or the kidneys. The predominantly reactive members of this group—avertin, paraldehyde, nembutal etc.—are excreted fairly rapidly; for they are excreted mainly after detoxication by the liver, while a considerably smaller proportion of the drug administered is excreted, unchanged, by the kidneys. A small proportion of ingested paraldehyde is also excreted, unchanged, by the lungs. Predominantly reactive, non-volatile anæsthetics may be administered by rectum for the production of basal anæsthesia. Predominantly non-reactive, non-volatile anæsthetics such as scopolamine, luminal, etc., on the other hand, are excreted fairly slowly; for the great part of the ingested drug is excreted, unchanged, by the kidneys; in clinical practice they are administered orally or by subcutaneous or intramuscular injection in single hypnotic doses.

It is clear that the rapidity and flexibility with which a given non-volatile blood-borne anæsthetic can be excreted from

must therefore be employed. Anæsthetic liquids and soluble solids may be injected directly into the venous circulation; they may be conveniently absorbed into circulating blood through the capillary bed of a hollow viscus such as the stomach or the rectum; or they may be injected subcutaneously or intramuscularly, to be absorbed from thence into circulating blood.

The three organs responsible for the excretion of blood-borne anæsthetics from circulating blood, and in turn from the body, are the lungs, the kidneys and the liver. The classification of blood-borne anæsthetics according to the mechanism of their excretion from circulating blood is a difficult problem. They fall roughly into two broad groups, viz.:

Non-reactive and Reactive Anæsthetics.

Non-reactive anæsthetics are excreted by the lungs or the kidneys, unchanged from the form in which they were absorbed. Reactive anæsthetics are detoxicated by oxidation, reduction, hydrolysis or conjugation, etc., probably in the liver, as a pre-requisite to the excretion of their harmless degradation products in the urine by the kidneys.

Volatile anæsthetics are non-reactive in character and are excreted almost entirely by the lungs, in the same form as that in which they were absorbed. An anæsthetic, however, that can pass through the glomerular membrane appears in the urine, for few (if any) anæsthetics are completely re-absorbed by the renal tubules. Traces therefore appear in the urine and, in point of fact, in all the secretions of the body; but the lungs are the main organs of excretion of volatile anæsthetics. Excretion by the lungs is flexible and rapid, and is a recapitulation in the reverse direction of their absorption into circulating blood. And the uptake and excretion of a volatile anæsthetic is so flexible and rapid that its concentration in circulating blood can be regulated in an upward and a downward direction in such a manner that it is suitable for the production of surgical anæsthesia in clinical practice.

Non-volatile non-reactive anæsthetics are excreted slowly in the urine by the kidneys in the same form that they were absorbed in. Their excretion cannot be wittingly hastened, but may be delayed when renal inefficiency is present, and the character of

CHAPTER VIII

THE ABSORPTION OF INHALATION ANÆSTHETICS BY THE BODY TAKEN AS A WHOLE

INHALATION anæsthetics are gases or vapours at body temperature. They are non-reactive substances: they do not react chemically with tissue cells or tissue fluids and they are excreted from the body via the respiratory system, unchanged from the form in which they were absorbed.[1]

In the conditions which obtain in clinical practice, anæsthetic gases and vapours obey the gas laws. A most characteristic property of a gas or vapour is its ability to expand until its composition and pressure are uniform throughout the space in which it is enclosed; when this result has been achieved the gas or vapour is in a state of equilibrium. This state of gaseous equilibrium is produced by the mass movement of the gases, i.e. by air currents, and/or by diffusion, for gases diffuse from a region of higher pressure to a region of lower pressure at a rate which is directly proportional to the diffusion gradient and inversely proportional to the square root of the density of the gas. A difference in gas pressure between two systems may therefore be equalised by the mass movement of gases, but when mass movement has reached the limit of its usefulness, diffusion goes on from the region of higher pressure to the region of lower pressure until gaseous equilibrium is established between two systems.

Described in its simplest terms, the absorption of an inhalation anæsthetic by Man's body consists of the assumption of a state of equilibrium in respect to the anæsthetic gas or vapour,

[1] Orcutt and Waters (1933) observed that 0 04 mgm. of nitrous oxide and 0 002 mgm of ethylene was excreted through each square cm. of skin surface per hour. An average adult has a skin surface of about 1 8 square metres, and about 736 mgm or 373 c.c. of nitrous oxide at N.T P. are excreted by skin diffusion per hour. It is even less in the case of ethylene, namely, 37 8 mgm or 30 c c at N.T.P., and the excretion of inhalation anæsthetics by skin, kidneys, etc., can be ignored.

circulating blood is largely responsible for the clinical method adopted to dissolve the particular anæsthetic in circulating blood. Uptake by and excretion from circulating blood combine characteristically to determine the exactness, speed and flexibility with which the blood concentration of a particular anæsthetic can be regulated—and these factors in turn determine the field of clinical usefulness of the particular anæsthetic.

It is proposed to discuss blood-borne anæsthetics in terms of their uptake by and excretion from circulating blood, together with the character of their absorption from circulating blood by the cells of the body, for this provides an explanation of their selective action on the brain, of the sequence in which specific types of brain cells are depressed, and of the methods to be adopted in clinical practice for the control of the action of blood-borne anæsthetics. Local anæsthetics are reactive and non-volatile anæsthetics. They are discussed in terms of their method of approach to the site of their drug fixation, their absorption from thence into circulating blood, the character of their uptake by tissue cells from circulating blood, and the mechanism of their excretion from the body.

in each sequence. In the first sequence, the failure of lung ventilation does not necessarily endanger life, or halt either the absorption and excretion of inhalation anæsthetics, or the uptake of oxygen and the excretion of carbon dioxide: for the mass movement of these gases can be effectively accomplished by artificial respiration. In point of fact, when controlled respiration is employed, the anæsthetist deliberately replaces the mass movement of normal lung ventilation with a form of mass movement of his own choosing. In contrast, the mass movement of inhalation anæsthetics by circulating blood in the second sequence cannot wittingly be influenced by the anæsthetist in an upward direction, but errors or accidents during anæsthesia may readily produce circulatory failure and at all times during anæsthesia the circulation must be maintained within the limits of normality by every means at the anæsthetist's disposal, for the uptake of oxygen and the excretion of carbon dioxide and inhalation anæsthetics cease when the mass movement of these gases by circulating blood fails.

For the purpose of description, the four phases of the absorption of inhalation anæsthetics by the body are discussed each as a complete and separate entity; but it is to be clearly understood that nothing could be farther from reality, for each successive phase is complementary to and continuous with the phase which preceeds it.

The First Phase of the absorption of inhalation anæsthetics by the body is constituted by the mass movement of these gases and vapours from the anæsthetic atmosphere to alveolar air and their diffusion throughout its entire volume.

Alveolar air is a physiological entity. In quiet breathing it has an average volume of 3,000 c.c. and consists of the gases and vapours in the depth of the lungs which are more or less in contact with the respiratory epithelium and which can carry out gaseous exchange with blood flowing in the pulmonary capillaries. is a reservoir of mixed gases and vapours whose total pressure l to the sum of the partial pressures of its contained gases rs. In normal conditions of life, the pressure of alveolar al with that of the atmosphere breathed, and at Mean s a total pressure of 760 mm. of mercury.

between the anæsthetic atmosphere and the cells of his w body. Absorption will be complete and the body saturated v *the tension of the anæsthetic in solution in the tissue cells of* whole body is equal to the pressure of the anæsthetic in the at phere to which the body is exposed. For example, when exp to an anæsthetic atmosphere containing nitrous oxide at a pa pressure of 600 mm. of mercury, the body will be saturated v it has dissolved sufficient nitrous oxide to raise the tension of gas in solution in the cells of the whole body to 600 mm mercury. The gas movement necessary to establish this stat gaseous equilibrium can be produced only by the mass m ment and/or the diffusion of gases from the anæsthetic at phere to the cells of the whole body. The absorption of an inh tion anæsthetic by the body may be conveniently considere two distinct sequences of events, each of which consists of a p *of mass movement and diffusion, followed by a diffusion solution phase.*

The first sequence results in the solution of the inhala anæsthetic in blood flowing in the pulmonary capillaries. Its phase is initiated by the *mass movement* of anæsthetic gases vapours, by lung ventilation, from the anæsthetic atmospher alveolar air; it is completed by *diffusion* of these gases vapours throughout the whole volume of alveolar air. second phase consists of the *diffusion* of anæsthetic gases vapours from alveolar air, through the respiratory membr and their solution in blood flowing in the pulmonary capillari

The second sequence results in the solution of the inhala anæsthetic in the tissue cells of the whole body. Its first ph is initiated by the *mass movement* of anæsthetic gases and vapo dissolved in blood, from the pulmonary capillaries to capillaries of the various organs of the body. The second ph consists of the *diffusion* of these gases and vapours from them *via* extracellular fluid, to be *dissolved* in the tissue cells in manner identical with that of the uptake of narcotics alrea described.

This artificial division of the mechanism of absorption of inha tion anæsthetics into two parts has been made to facilit description and to emphasise the importance of mass movem

and upwards and the thorax is enlarged in its lateral and horizontal diameters.

The action of the abdominal muscles on inspiration is mainly instrumental in determining the character of the co-ordinate action of the muscles of inspiration; in normal conditions of life two types of breathing are observed, viz. costal and diaphragmatic breathing. In costal breathing, the relaxed condition of the recti on inspiration permits the costal margin, which is the origin of the sterno-costal fibres of the diaphragm, to move cranially; when the diaphragm contracts its movement is directed *mainly forward*, and its action on the abdominal contents is relatively slight. In diaphragmatic breathing, the tone of the recti on inspiration or their active contraction tends to fix the costal margin and prevent its movement cranially and in this instance, when the diaphragm contracts, it *drives downwards and forwards*, pushing the abdominal contents before it. Women are usually costal breathers. The diaphragmatic type of breathing is common in children, in men, in old age (when the thorax becomes less flexible), and in both sexes when the supine position is adopted.

The action of the diaphragm thus depends upon which group of muscles acts as its antagonist. During deep anæsthesia, when muscle tone has been abolished in both the abdominal and the intercostal muscles, breathing assumes a jerky character and this jerky inspiratory effort is associated with a tracheal tug. A tracheal tug has long been associated with anæsthesia deep enough to paralyse the intercostal muscles and has been attributed to the ineffective contraction of the sternocostal fibres of the diaphragm, for under these conditions—because of the toneless condition of the abdominal and intercostal muscles—the origin of the sterno-costal fibres, the costal margin, is no longer a fixed fulcrum on inspiration. In consequence, the action of the crural fibres of the diaphragm becomes more apparent and on inspiration they pull—through the central tendon and in turn the pericardium—on the roots of the lungs, displacing the whole bronchial tree caudally with each inspiratory phase of respiration.

Keith (1909) states that, " the diaphragm is made up of two parts (sternocostal and crural) which are different in origin, different in their nerve supply and different in their action." He

Evolutionary development has separated these two gas systems, viz. alveolar air and the atmosphere breathed, from one another; they communicate through a narrow tube consisting of the naso-bucco-pharynx, the trachea and the bronchi. This narrow tube, which has an average volume of 150 c.c. and is called the "dead space of the respiratory tract," renders the diffusion of gases *an inadequate means* of equalising the gas pressure between these two systems at a sufficient rate to satisfy the metabolic needs of a resting man. In normal conditions of life the mass movement of gases by lung ventilation is, therefore, essential if the excretion of carbon dioxide on expiration and the intake of oxygen on inspiration are to satisfy the requirements of a man, even when he is at rest.

Breathing, the act by which lung ventilation produces the mass movement of gases sufficient to permit the free and rapid interchange of gases between atmospheric and alveolar air, is accomplished without any special volition but may be greatly modified by psychic influences. In quiet breathing, a unit respiratory effort in an average normal adult consists of an inspiratory phase of 500 c.c., followed by an expiratory phase of corresponding volume; this unit respiratory effort is repeated rhythmically 16-18 times per minute The rate of respiration in a new-born babe is about 44 breaths per minute, but with advancing years the respiratory rate slows: it is 26 breaths per minute in a child of 5 years, and has fallen to 18 breaths per minute at the age of 20 years.

Inspiration, essentially an active process, is produced by the co-ordinate action of the diaphragm, the thoracic and the abdominal musculature.

The diaphragm is the most important muscle of inspiration. It is a thin musculo-fibrous partition separating the thorax from the abdomen. When it contracts, the diaphragm as a whole flattens and in the manner of a piston it enlarges the thorax in its vertical diameter

When the inspiratory muscles of the thorax contract, the ribs, which are hinged on the articulations of their vertebral bodies and the tubercule of their transverse processes, swing forwards

greatest at the end of inspiration, when it amounts to—9 mm. of mercury, and smallest at the end of expiration, when it measures —7·5 mm. of mercury. In the presence of a normal negative intrapleural pressure, when the thorax enlarges, the lungs increase in volume and the bronchial tree dilates and lengthens.

Expiration, like inspiration, is an active process. When the inspiratory muscles lose their tone, the elastic recoil of the costal cartilages, the contraction of the muscles of expiration, and the controlled relaxation of the diaphragm, all combine to return the thorax to the position of expiration; and the lungs, by reason of the diminished capacity of the thoracic cage and their own elasticity, are reduced in volume, and the bronchial tree shortens and narrows.

Such, briefly, is the mechanism of the mass movement of gases by lung ventilation. In the presence of a normal negative intrapleural pressure an increase or a decrease in the capacity of the thorax is followed by a corresponding increase or decrease in the volume of the lungs. Since the lungs communicate freely with the atmosphere to which the body is exposed, it follows that the volume of this atmosphere moved to or from the lungs with the phases of respiration varies with the movements of the thoracic cage, and that intrapulmonary pressure always equals the pressure of the atmosphere to which the body is exposed.[1]

The volume of the mass movement of gases by lung ventilation is controlled by the respiratory centre, in normal conditions of life, it is proportional to the metabolic rate of the subject. In quiet breathing, 500 c c. of air are carried to and expelled from the lungs at each unit respiratory effort. This is termed Tidal Air. After a quiet expiration of 500 c.c., an additional volume of 1500 c c can be expelled from the lungs by the greatest possible expiratory effort. This is called Supplemental Air. After this greatest possible expiration, however, there still remain in the lungs 1500 c.c. of Residual Air, which can be expelled only if negative intrapleural pressure is abolished, when the lungs—no

[1] When inspiration commences, the delayed opening of the glottis ("the glottic lag") is responsible for a slight negative intrapulmonary pressure early in inspiration, but, in the absence of respiratory obstruction, intrapulmonary pressure at the end of inspiration always equals that of the atmosphere to which the body is exposed

observed in patients who were described clinically as neurasthenics, that the spinal or crural part of the diaphragm may act forcibly while the sternocostal part is almost passive. Miss S. Evans, Sister in Charge of the Massage Department of Guy's Hospital, has also observed this phenomenon in nervous subjects, and the author has observed the overaction of the crural part of the diaphragm with a tracheal tug in curarised subjects, whether the subject is anæsthetised or not. Moreover, it has been possible, through the co-operation of the surgeons, to study the action of the diaphragm during a laparotomy in a number of curarised, anæsthetised subjects. Observations show that when a tracheal tug is present the sternocostal part of the diaphragm is quite passive on inspiration and diaphragmatic action is confined solely to its crural fibres. During anæsthesia deep enough to paralyse the intercostal muscles, or when curarization is carried to the level of intercostal paralysis, it seems clear that the jerky inspiratory effort, with a tracheal tug, is caused by the forcible action of the crural fibres of the diaphragm combined with completely passive sternocostal fibres of this muscle. This in turn suggests that Keith's thesis of the common origin, nerve supply and action of the intercostal muscles and the sternocostal fibres of the diaphragm will bear re-examination.

In each type of breathing the muscular effort of inspiration results in an enlargement of the thorax, and the movements of the thoracic cage are transmitted to the lungs through negative intrapleural pressure. The pleural cavity is a narrow space which normally contains just sufficient fluid to act as a lubricant and to allow the visceral pleura to move freely over the parietal pleura during the movements of breathing. The apposition of the moistened surfaces of the visceral and parietal pleura tend to hold the lungs against the chest wall so that its movements are communicated to the lungs. The so-called negative intrapleural pressure is therefore the resultant of two forces: one being the elasticity of the lungs, which are always attempting to collapse and so pull away from the chest wall, and the other the strong adhesive force of the moistened visceral and parietal pleura, which tends to hold the lungs in apposition with the chest wall. In normal conditions of life, the negative intrapleural pressure is

depth of breathing in the same individual. In quiet breathing, effective dead space coincides more or less accurately with the volume of anatomical dead space and has an average volume of 150 c.c.; but, as breathing deepens, it increases in volume until—when at length the vital capacity of the subject is reached—it

TABLE 14.

THE INFLUENCE OF DEAD SPACE ON THE VOLUME OF EFFECTIVE LUNG VENTILATION.

Inspiration	–	Effective Dead Space	=	Effective Lung Ventilation
500 c.c.	–	150 c.c.	=	350 c.c.
3500 c.c.	–	600 c.c.	=	2290 c.c.
150 c.c	–	150 c c.	=	Zero
Inspiration – (Effective D S. + Artificial D.S.) = Effective L.V.				
3500 c c – (600 c c. + 2900 c.c.) = Zero.				

has a volume of about 600 c.c. The dead space of the respiratory tract is therefore a factor of considerable importance, *for it not only makes the mass movement of gases by lung ventilation imperative but it also reduces the effectiveness of the mass of gases moved in this manner.*

Reference to Table 14 shows that in quiet breathing, when on inspiration 500 c.c. of gas enter the respiratory system, only 350 c.c. of this amount actually enter alveolar air, and that when the inspiratory effort has increased to 3500 c.c., the volume of effective lung ventilation is 2900 c.c. During shallow breathing, if the volume of the inspiratory effort is less than 150 c.c., the muscular effort of breathing produces no mass movement of gases to alveolar air, and the volume of effective lung ventilation is reduced to zero. An identical result is obtained when the volume of artificial dead space exceeds 2900 c.c.—which may occur in a badly designed closed system of breathing—for, when the muscular effort of breathing is the greatest possible, the mass of gases moved from the anæsthetic atmosphere to alveolar air is nil and the volume of effective lung ventilation is therefore zero.

longer supported by their adhesion to the chest wall—completel collapse by virtue of their own elasticity. Reference to Figure shows that, in quiet breathing, alveolar air has a volume of 300 c.c. and consists of the sum of residual and supplemental ai After an inspiration of 500 c.c. an additional volume of 1500 c.c

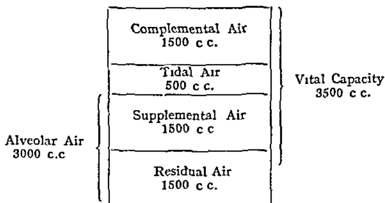


FIGURE 6.

can be inspired by the greatest possible inspiratory effort. Th is termed Complemental Air. Figure 6 shows that the greate volume of air that can be inspired after the greatest possib expiration is the sum of supplemental, tidal and complemental ai It amounts to 3500 c.c. in an average healthy adult, and is terme the Vital Capacity of the subject.

Hence, in response to the metabolic needs of the subject th mass movement of gases by lung ventilation at each un respiratory effort varies, in normal conditions of life, between th lower limit of 500 c c. and the upper limit of 3500 c.c.

These figures represent the volume of gas entering and leavin the respiratory system at each unit respiratory effort. They do no however, represent the volume of gas actually entering and leavin alveolar air, for a proportion of any given respiratory effort lodg in the dead space of the respiratory tract and is consequentl ineffective as a means of modifying the gas content of alveolar ai

It has been shown that the bronchial tract moves rhythmicall during the phases of respiration, lengthening and dilating o inspiration and shortening and narrowing during expiration. Th physiological entity, EFFECTIVE DEAD SPACE, therefore varies wit

Mass movement having reached the limit of its usefulness, diffusion goes on until the nitrous oxide pressure is uniform throughout the whole 4400 c.c. of alveolar air and is achieved when the nitrous oxide pressure throughout is 375 mm. of mercury. For:

$$p' \times 4400 = \underset{\text{Residual Air}}{(1500 \times 0)} + \underbrace{\left[\underset{\textit{from Dead Space}}{(150 \times 0)} + \underset{\textit{from Anæsthetic Atmosphere}}{(2750 \times 600)}\right]}_{\text{Effective Lung Ventilation}} \quad \text{Boyle's Law}$$

$$p' = 375 \text{ mm. of Hg.}$$

On expiration, 3500 c.c. are expelled from the respiratory system; 600 c.c. from the dead space of the respiratory tract and 2900 c.c. from the lung alveoli. At the end of this first unit respiratory effort, the respiratory system contains 1500 c.c. of residual air whose nitrous oxide pressure is 375 mm. of mercury, and 150 c.c. of nitrous oxide at 375 mm. of mercury in the now shortened and narrowed dead space.

At the second inspiration after exposure to this anæsthetic atmosphere, 3500 c.c. again enter the respiratory system; of this volume, 2900 c.c. of effective lung ventilation consisting of 150 c c. (nitrous oxide pressure, 375 mm. of mercury) from the dead space of the respiratory tract, and 2750 c.c. of anæsthetic atmosphere (nitrous oxide pressure, 600 mm. of mercury) enter the lungs; and the remaining 600 c.c. (at a nitrous oxide pressure of 600 mm. of mercury) lodge in the now dilated dead space of the respiratory tract. At the end of this second inspiration after exposure to this anæsthetic atmosphere, the lung alveoli contain 1500 c.c. of residual air (nitrous oxide pressure, 375 mm. of mercury), 150 c.c. of dead space air (nitrous oxide pressure, 375 mm. of mercury), and 2750 c.c. of anæsthetic atmosphere (nitrous oxide pressure, 600 mm. of mercury). When gaseous equilibrium has been assumed throughout the whole volume of alveolar air, the nitrous oxide pressure is 515·6 mm. of mercury for:

$$p' \times 4400 = (1500 \times 375) + \left[(150 \times 375) + (2750 \times 600)\right]$$
$$\text{and } p' = 515{\cdot}6 \text{ mm. of Hg.}$$

At the end of this second unit respiratory effort, the pressure of nitrous oxide in alveolar air has risen to 515.6 mm. of mercury.

The rapidity with which the mass movement of gases by lung ventilation produces a state of gaseous equilibrium between the anæsthetic atmosphere and alveolar air depends upon the volume of effective lung ventilation, which in turn depends upon the depth of breathing. The larger the volume of effective lung ventilation the more rapidly will gaseous equilibrium be assumed between these two systems.

Suppose a man at Mean Sea Level is exposed to an anæsthetic atmosphere containing nitrous oxide at a partial pressure of 600 mm. of mercury and oxygen at a partial pressure of 160 mm. of mercury. Since the respiratory and anæsthetic gases and vapours in common clinical use do not react chemically with one another, each gas and each vapour behave as independent entities and reach a state of equilibrium in the two gas systems, viz. the anæsthetic atmosphere and alveolar air, un-influenced by the presence of other gases and vapours in these two gas systems. And if (for the purpose of description) we ignore the second phase of this sequence of absorption and the water vapour and carbon dioxide content of the alveolar air, then the mechanism of the assumption of gaseous equilibrium between the nitrous oxide content of the anæsthetic atmosphere and alveolar air is as follows:

When breathing is the deepest possible, the volume of the inspiratory effort is 3500 c.c. and it is assumed that the dead space of the respiratory tract expands to about 600 c.c. at full inspiration and contracts to about 150 c.c. at the end of expiration. Of the 3500 c c. which enter the respiratory system at the first inspiration after exposure to this anæsthetic atmosphere, 2900 c.c. of effective lung ventilation—consisting of 150 c.c. of nitrous oxide-free air contained in the dead space of the respiratory tract and 2750 c.c. of anæsthetic atmosphere whose nitrous oxide pressure is 600 mm. of mercury—enter the lungs and the remaining 600 c.c. whose nitrous oxide pressure is 600 mm. of mercury, lodge in the now dilated and lengthened dead space of the respiratory tract.

Thus, at the end of the first inspiration after exposure to this anæsthetic atmosphere, the lung alveoli contain 1500 c.c. of nitrous oxide-free residual air, 150 c.c of nitrous oxide-free air from the dead space of the respiratory tract, and 2750 c c of anæsthetic atmosphere whose nitrous oxide pressure is 600 mm. of mercury.

At the second inspiration after exposure to this anæsthetic atmosphere, 500 c.c. again enter the respiratory system and of this, 350 c.c. of effective lung ventilation—consisting of 150 c.c. of dead space air (nitrous oxide pressure of 35·5 mm. of mercury) and 200 c.c. of anæsthetic atmosphere (nitrous oxide pressure of 600 mm. of mercury)—enter the lung alveoli, and the remaining 150 c.c. (nitrous oxide pressure of 600 mm. of mercury) lodge in the dead space of the respiratory tract. At the end of this second inspiration, the lung alveoli contain 3000 c.c. of alveolar air (nitrous oxide pressure of 35·5 mm. of mercury), 150 c.c. of dead space air (nitrous oxide pressure of 35·5 mm. of mercury) and 200 c.c. of anæsthetic atmosphere (nitrous oxide pressure of 600 mm. of mercury). When gaseous equilibrium in respect to nitrous oxide has been achieved throughout alveolar air, the pressure of nitrous oxide has risen to 69·2 mm. of mercury, for:

$$p' \times 3500 = (3000 \times 35\ 5) + \left[(150 \times 35\ 5) + (200 \times 600)\right]$$
$$p' = 69\ 2 \text{ mm. of Hg.}$$

At the end of the second breath, the pressure of nitrous oxide in alveolar air has risen to 69 2 mm. of mercury.

		Mm. of Hg.
After three breaths to	.. ..	100
After four breaths to	.. ..	136·6
After five breaths to	... 25% saturation ...	158 6
After twelve breaths to . .	50% saturation ...	313
After twenty three breaths to	. 75% saturation	454
After ninety breaths to	. . ..	599 6

And in the conditions specified, anæsthetic equilibrium in respect to nitrous oxide has virtually been achieved between the anæsthetic atmosphere and alveolar air in about 90 breaths after exposure to this anæsthetic atmosphere.

Comparison of the deepest possible breathing with quiet breathing, shown graphically in Figure 7, illustrates the influence which variations in the minute volume of effective lung ventilation exercise on the rate at which alveolar air attains gaseous equilibrium with an anæsthetic atmosphere of constant composition. At a uniform respiratory rate of 18 breaths per minute, in the hypothetical example quoted above, equilibrium between these

	Mm of I
At the end of the third breath it has risen to ...	568·3
After four breaths to	588·1
After five breaths to	595·5
After six breaths to	598·3
After seven breaths to	599·3
After eight breaths to	599 7
After nine breaths to	599 8
After ten breaths to	599·9

And in the conditions specified, anæsthetic equilibrium in respect nitrous oxide has virtually been achieved between the anæsthe atmosphere and alveolar air, in about ten breaths after expos to this anæsthetic atmosphere.

In quiet breathing, when the volume of the inspiratory eff is 500 c.c , the dead space of the respiratory tract has a volu of about 150 c.c., which it is assumed does not alter materia during inspiration and expiration. In quiet breathing at the fi inspiration after exposure to this same anæsthetic atmosphe 500 c.c. of this atmosphere enters the respiratory system and this 350 c.c. of effective lung ventilation—consisting of 150 c.c. nitrous oxide-free air from the dead space of the respiratory tr and 200 c.c. of anæsthetic atmosphere containing nitrous oxide a pressure of 600 mm. of mercury—enter the lungs, and t remaining 150 c c. whose nitrous oxide pressure is 600 mm. mercury lodge in the dead space of the respiratory tract. Th at the end of the first inspiration after exposure to this anæsthe atmosphere, the lung alveoli contain 3000 c.c. of nitrous oxic free alveolar air, 150 c c. of nitrous oxide-free air from the de space of the respiratory tract and 200 c.c. of anæsthetic atm phere whose nitrous oxide pressure is 600 mm. of mercury. Wh the nitrous oxide pressure is uniform throughout the whole 33 c.c. of alveolar air the pressure of nitrous oxide is 35.5 mm. mercury, for:—

$$p' \times 3500 = \underset{\text{Alveolar Air}}{(3000 \times 0)} + \Big[\underbrace{\underset{\textit{from}\text{ Dead Space}}{(150 \times 0)} + \underset{\textit{from}\text{ Anæsthetic Atmosphere}}{(200 \times 600)}}_{\text{Effective Lung Ventilation}} \Big] \text{Boyle's La}$$

and $p' = 35\ 5$ mm of Hg

If the blood in the pulmonary capillaries remained in contact with the respiratory membrane for an unlimited time, gaseous equilibrium between the gas content of alveolar air and that of blood flowing in the pulmonary capillaries would invariably be achieved. In this instance, the mass of a given anæsthetic gas or vapour dissolved in blood leaving the lungs would vary directly as its partial pressure in alveolar air.

In normal conditions of life, however, blood flowing in the pulmonary capillaries remains in contact with the respiratory membrane for a time which varies between 0·5 and 1·0 seconds. This limitation of the period of contact of blood with the respiratory membrane makes the velocity of diffusion of a particular gas or vapour through this membrane a dominant factor in determining whether it is possible for this gas or vapour to attain gaseous equilibrium, between alveolar air and blood flowing in the pulmonary capillaries, in the time available for gaseous exchange.

The rate of diffusion of a gas or vapour is directly proportional to its diffusion gradient and inversely proportional to the square root of its density. Exner observed that the rate of diffusion of gases through a thin fluid film was directly proportional to the solubility of the gas in the fluid film and inversely proportional to the square root of the density of the gas. As the respiratory membrane can be looked upon as a thin watery film, these properties of a particular gas or vapour, together with the thickness of the respiratory membrane and the area of lung, combine to determine the velocity of diffusion of a gas or vapour through the respiratory membrane. The diffusion velocity can be calculated from the following formula:

$$\text{Diffusion velocity} = \frac{\text{Pressure gradient} \times \text{Solubility of gas}}{\text{Density of gas.}} \times K,$$

$$\text{where } K = \frac{0\ 139 \times \text{Area of lung}}{\text{Thickness of lung.}}$$

Table 15 shows that, at a resting metabolic rate, the pressure gradient between the carbon dioxide content of mixed venous blood and alveolar air is 6 mm. of mercury. Its coefficient of solubility in 100 c.c. of water is 55·5 c.c., and its vapour density is 22. The iffusion velocity of carbon dioxide from blood flowing in the

two gas systems would be achieved in a little more than half a minute when breathing is the deepest possible (Curve A): in quiet breathing (Curve B) the same result would take about five minutes to achieve. The water vapour and carbon dioxide content of alveolar air, and the loss of anæsthetic to blood flowing in the

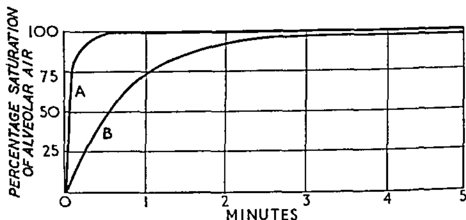


FIGURE 7.

The rate of saturation of alveolar air with an anæsthetic atmosphere of constant composition.

pulmonary capillaries, will retard the rate at which gaseous equilibrium is assumed; but it is clear that an increase in the volume of lung ventilation and/or the respiratory rate will materially hasten the rate at which gaseous equilibrium is assumed between alveolar air and an anæsthetic atmosphere of constant composition.

The SECOND PHASE of the absorption of inhalation anæsthetics by the body is constituted by the diffusion of these gases and vapours from alveolar air, through the respiratory membrane, and their solution in blood flowing in the pulmonary capillaries.

Mixed venous blood on entering the pulmonary capillaries suddenly spreads out into a layer not more than one corpuscle thick, and by so doing exposes to the respiratory membrane a thin layer of blood with an area about 1000 square feet. In normal health, the respiratory membrane which separates this huge thin area of blood from alveolar air is 0·004 mm. thick; clearly, such circumstances are favourable for gaseous exchange between the gas content of alveolar air and that of blood flowing in the pulmonary capillaries.

alveolar air and blood flowing in the pulmonary capillaries in the 0·5 - 1·0 seconds available for gaseous exchange between these two systems.

Of the three factors which in normal conditions of life are responsible for the diffusion velocity of these respiratory gases through the respiratory membrane, two—the vapour density and the water solubility—are physical constants, and the remaining factor—the pressure gradient—is a variable. The vapour densities of oxygen and carbon dioxide, viz. 16 and 22 respectively, are sufficiently alike to be of little relative influence. On the other hand the influence of water solubility is seen to be a dominant one. In spite of the fact that the diffusion gradient of carbon dioxide is one-tenth that of oxygen, its diffusion velocity through the respiratory membrane is twice that of oxygen, and reference to the above figures shows that this must be attributed to the fact that carbon dioxide is almost 25 times more soluble than oxygen in the respiratory membrane, i.e. in water. The diffusion gradient of oxygen must be raised to 120 mm. of mercury to produce a diffusion velocity through the respiratory membrane equal to that of carbon dioxide at a resting metabolic rate.

These three factors, in like manner, are responsible for the rate of diffusion of inhalation anæsthetics through the respiratory membrane; and the diffusion velocities of oxygen and carbon dioxide through this membrane may be used as standards to assess the diffusion velocities through the respiratory membrane of the common inhalation anæsthetics.

Table 16 shows that the vapour densities of oxygen, carbon dioxide and the common clinical inhalation anæsthetics lie between 13 and 37, excepting only chloroform and trichlorethylene, whose vapour densities are respectively 59 5 and 65·5. Since the influence of vapour density on diffusion is inversely proportional to the square root of this index, it is clear that in general the densities of the inhalation anæsthetics in common clinical use have little relative influence on their diffusion velocities through the respiratory membrane; but in the case of chloroform and trichlorethylene a high vapour density is in part responsible for their slow rate of diffusion through the respiratory membrane, relative to that of oxygen and carbon dioxide.

pulmonary capillaries, through the respiratory membrane (considered as a watery film) to alveolar air is therefore 70 K for:

$$\frac{6 \times 55{\cdot}5}{\sqrt{22}} = 70\text{K}$$

TABLE 15.

AVERAGE TENSION OF RESPIRATORY GASES.

	TENSION OF OXYGEN	TENSION OF CARBON DIOXIDE
Mixed venous blood (at rest)	40 mm. of Hg	46 mm. of Hg.
Alveolar air	100 mm. of Hg.	40 mm. of Hg.
Arterial blood	80-90 mm. of Hg.	40 mm of Hg.

Reference to Table 15 also shows that the carbon dioxide tensions in alveolar air and arterial blood are at 40 mm. of mercury identical, in normal conditions of life it is clear that the diffusion velocity of carbon dioxide through the respiratory membrane, viz. 70 K, is sufficiently rapid to allow gaseous equilibrium to be assumed between the carbon dioxide content of these two systems in the time available for gaseous exchange.

Table 15 also shows that in normal conditions of life the pressure gradient between oxygen in alveolar air and mixed venous blood is 60 mm. of mercury. Its coefficient of solubility in 100 c.c. of water is 2 37 c.c., and its vapour density is 16. The diffusion velocity of oxygen from alveolar air, through the respiratory membrane to blood flowing in the pulmonary capillaries, is therefore 35 K, for:

$$\frac{60 \times 2\ 37}{\sqrt{16}} = 35\text{K}$$

Observations in normal subjects have shown that the tension of oxygen in arterial blood is invariably lower by 10 - 20 mm. of mercury than that of alveolar air and there is little doubt that oxygen diffuses with difficulty through the respiratory membrane. Table 15 illustrates this point and shows that a diffusion velocity of 35 K, oxygen fails to attain gaseous equilibrium between

that of carbon dioxide, viz. 70 K. when its diffusion gradient is 37 mm. of mercury, and its diffusion gradient falls to 37 mm. of mercury when the body is 90% (circa) saturated to the partial pressure of ethylene commonly used in clinical practice.

It can be concluded that the diffusion velocities of all the common inhalation anæsthetics, except cyclopropane, chloroform and

TABLE 16.

THE DIFFUSION VELOCITY OF THE RESPIRATORY AND ANÆSTHETIC GASES AND VAPOURS.

	Vapour Density	Solubility in 100 c.c. of water at 37° C	Diffusion Velocity at a diffusion gradient of 60 mm. of Hg.	Diffusion Velocity at a diffusion gradient of 6 mm. of Hg.
Di-ethyl ether	37	1546 c.c.	14700 K	1470 K
Di-vinyl ether	14	—	—	—
Ethyl chloride	32	253 36 c c.	2676 K	267 6 K
Acetylene	13	74·3 c c.	1236 K	123 6 K
Carbon dioxide	22	55 5 c.c	—	70 K
Nitrous oxide	22	39 5 c c	504 K	50·4 K
Ethylene	14	7 3 c.c.	114 K	11·4 K
Oxygen	16	2.37 c c	35 K	—
Cyclopropane	21	0 514 c c.	6·6 K	0·66 K
Chloroform	59 5	0 42 c.c.	3·3 K	0·33 K
Trichlorethylene	65 5	—	—	—

trichlorethylene, through the respiratory membrane, are sufficiently rapid to permit gaseous equilibrium to be assumed between the anæsthetic content of alveolar air and blood flowing in the pulmonary capillaries in the time available for gaseous exchange between these two systems.

Inhalation anæsthetics obey Henry's law in the conditions obtaining in clinical practice, and Table 17 shows the coefficient of solubility of the common inhalation anæsthetics in 1 c.c. of water and of whole blood. This index represents the volume of anæsthetic gas or vapour dissolved in the solvent when the tension of the anæsthetic in solution is equal to the partial pressure of the anæsthetic to which the solvent is exposed. Accurate determinations of these constants at body temperature are essential to

The influence of the water solubility of inhalation anæsthetics on their diffusion velocities through the respiratory membrane is however a dominant one. In Table 16 oxygen, carbon dioxide and the common inhalation anæsthetics are arranged in the order of their solubility in water, and it is seen that this too is the order of their diffusion velocities through the respiratory membrane. It is seen that when the diffusion gradient is 60 mm. of mercury only cyclopropane, chloroform and trichlorethylene—whose water solubility is lower than that of chloroform—have a diffusion velocity less than that of oxygen; and it can be concluded that these three inhalation anæsthetics diffuse with difficulty through the respiratory membrane and fail to assume a state of gaseous equilibrium between alveolar air and blood flowing in the pulmonary capillaries in the time available for gaseous exchange between these two systems. At a diffusion gradient of 6mm. of mercury, di-ethyl ether, ethyl chloride, acetylene—and probably di-vinyl ether whose physical properties are similar to those of di-ethyl ether—have diffusion velocities greater than that of carbon dioxide; these anæsthetics without doubt invariably do assume a state of gaseous equilibrium between alveolar air and blood flowing in the pulmonary capillaries in the time available for gaseous exchange. Nitrous oxide and ethylene have diffusion velocities through the respiratory membrane more than three times that of oxygen at a diffusion gradient of 60 mm. of mercury and less than that of carbon dioxide at a diffusion gradient of 6 mm of mercury. If the diffusion gradient of nitrous oxide is increased to 9 mm of mercury its diffusion velocity through the respiratory membrane is equal to that of carbon dioxide, viz. 70 K. At a partial pressure of 600 mm. of mercury of nitrous oxide in the anæsthetic atmosphere, the diffusion gradient of nitrous oxide in alveolar air falls below 9 mm. of mercury only when the body is 99·5% (circa) saturated, and it can be concluded that in clinical practice the diffusion velocity of nitrous oxide through the respiratory membrane is sufficiently rapid to permit a state of equilibrium between the nitrous oxide content of alveolar air and blood flowing in the pulmonary capillaries in the time available for gaseous exchange. The same is probably true of ethylene, for its diffusion velocity through the respiratory membrane equals

TABLE 17.

COEFFICIENT OF SOLUBILITY OF THE ANÆSTHETICS IN COMMON CLINICAL USE.

Anæsthetic	Coefficient of Solubility in water.	Oil/Water partition coefficient	Coefficient of Solubility in Whole Blood	
Di-ethyl ether	15 46 c.c	2 3	15 c c	Henderson & Haggard (1927)
Di-vinyl ether	—	2 5	—	Leake & Chen (1930)
Ethyl chloride	2 35 c c	—	2·5 c c.	Nicloux *et al* (1934)
Acetylene	0 743 c c	1 89	0 741 c c	Schoen (1923)
Nitrous oxide	0 395 c c.	3 4	0 412 c c	Siebeck (1909)
Ethylene	0 073 c c	13	0 118 c.c.	Nicloux *et al* (1934)
Cyclopropane	0 00514 c.c	43	0·0115 c.c.	Waters (1936)
Chloroform	0 0042 c.c.	64	0·0142 c.c.*	Winterstein (1926)
Trichlorethylene	—	—	—	

* This value is thought to be too high.

any discussion of the behaviour of anæsthetic gases and vapours, but the figures shown in Table 17 were observed some at room temperature and some at body temperature. These constants are not available for di-vinyl ether, but Kockman (1936) states that the solubility of di-vinyl ether in water and in whole blood may be presumed to be similar to that of di-ethyl ether. Leake and Chen (1930) state that the oil/water partition coefficient of di-vinyl ether is of the value of 2·5, but Adriani (1946) gives the value of this index as 41·3. Other authorities are also at variance, for Winterstein (1926) gives the coefficient of solubility of chloroform in whole blood as 0·0142 c.c., but the figure of Nicloux for this index is 0 0152 c.c. Again, Embling (1906) states that the coefficient of solubility of ethyl chloride in whole blood is greater than 5 c.c., while Nicloux *et al* give 2·5 c.c. as the value of this index. As Henderson and Haggard pointed out 20 years ago, there is a great need for the systematic determination of the solubility coefficients of all the more volatile substances in water and in blood at body temperature, together with their possible combinations with hæmoglobin, for while there is no agreement there is much evidence to suggest that chloroform, nitrous oxide etc., actually combine with hæmoglobin.

Henderson and Haggard (1927) state that " in general, the solubility of a gas in blood is only slightly less than its solubility in water." Reference to Table 17, however, shows that this is true only of gases and vapours with a low oil/water partition coefficient. Of the common anæsthetic gases and vapours cited in this table, it is seen that those with an oil-water partition coefficient of 3·4 and greater, are more soluble in whole blood than in water: the greater this index, the greater is the solubility in whole blood relative to that in water. This is attributed to the lipoid content of the red blood corpuscles. The following observations of the coefficients of solubility of nitrous oxide, which has an oil/water partition coefficient of 3 4—quoted by Kockman (1936) from the work of Schoen (1923) and Siebeck (1909)—illustrate the point.

Coefficient of solubility of nitrous oxide at 37°C in		
	water	0 395 c c.
	plasma (human)	0·385 c.c
	erythrocytes (human)	0 446 c.c.
	whole blood (human)	0.412 c c

It follows that alveolar air loses 185·4 c.c. of nitrous oxide at 600 mm. of mercury or less to circulating blood every 3 seconds, while it receives from the anæsthetic atmosphere, during the same time, 350 c.c. of nitrous oxide at 600 mm. of mercury.

The coefficient of solubility of ethylene in whole blood at body temperature is smaller than that of nitrous oxide, and its diffusion velocity through the respiratory membrane is sufficiently rapid to permit gaseous equilibrium to be assumed between alveolar air and blood flowing in the pulmonary capillaries in the time available for gaseous exchange between these two systems. It can be concluded that equilibrium between alveolar air and an anæsthetic atmosphere containing nitrous oxide or ethylene is rapidly achieved and, once achieved, the tension of nitrous oxide or ethylene in blood leaving the pulmonary capillaries is equal to the partial pressure of these gases in the anæsthetic atmosphere to which the body is exposed.

The coefficient of solubility of cyclopropane, chloroform and trichlorethylene in whole blood at body temperature is smaller even than that of ethylene, and it follows that equilibrium between an anæsthetic atmosphere containing any one of these three anæsthetics and alveolar air is rapidly achieved. The diffusion velocities of these three anæsthetics through the respiratory membrane are, however, too sluggish to permit anæsthetic equilibrium to be assumed between alveolar air and blood flowing in the pulmonary capillaries in the time available for gaseous exchange between these two systems: equilibrium having been achieved between the anæsthetic atmosphere and alveolar air, the tension of these three anæsthetics in blood leaving the pulmonary capillaries is always less than the partial pressure of these anæsthetics in alveolar air and in turn in the anæsthetic atmosphere to which the body is exposed

On the other hand, di-ethyl and di-vinyl ether and ethyl chloride, whose diffusion velocities through the respiratory membrane are very rapid—more rapid even than that of carbon dioxide—have such a large coefficient of solubility in whole blood at body temperature, that the pressure of the anæsthetic in alveolar air is *very materially reduced* by the solution of the mass of

It is seen that the solubility of nitrous oxide in plasma is less than in water; this is due to the presence of salts in solution in plasma. The lipoid content of erythocytes—and perhaps their hæmoglobin content—is responsible for the increased solubility, and whole blood with a normal hæmocrit dissolves more nitrous oxide than does an equal volume of water.

The coefficient of solubility of certain inhalation anæsthetics in whole blood at 37°C. is so small that the mass of anæsthetic dissolved in blood flowing in the pulmonary capillaries per unit time is less than the mass of anæsthetic carried by effective lung ventilation to alveolar air during the same time. When this is so, two important consequences follow: (1) gaseous equilibrium between the anæsthetic atmosphere and alveolar air is *rapidly* achieved and (2) when once gaseous equilibrium has been achieved between these two systems, the partial pressure of the anæsthetic in alveolar air is not *significantly* reduced by the mass of anæsthetic which can be dissolved in blood flowing in the pulmonary capillaries per unit time.

Suppose a subject with a uniform circulatory rate of 9 litres per minute, breathing quietly at 18 breaths per minute, is exposed to an anæsthetic atmosphere containing nitrous oxide at a partial pressure of 600 mm. of mercury. At each unit respiratory effort, after anæsthetic equilibrium has been achieved between this anæsthetic atmosphere and alveolar air, the lungs receive 350 c.c. of nitrous oxide at 600 mm. of mercury. At this rate of breathing a unit respiratory effort occupies about 3 seconds, and at the circulatory rate specified during this period of time, 450 c.c. of mixed venous blood are exposed to the respiratory membrane and can carry out gaseous exchange with alveolar air. The coefficient of solubility of nitrous oxide in whole blood at body temperature is 0 412 c c , and 450 c c., of blood dissolve 0 412 × 450 = 185 4 c.c. of nitrous oxide at 600 mm. of mercury, when fully saturated to the pressure of nitrous oxide in the anæsthetic atmosphere to which it is exposed. The diffusion velocity of nitrous oxide through the respiratory membrane is sufficiently rapid to permit gaseous equilibrium to be assumed between the nitrous content of alveolar air and blood flowing in the pulmonary capillaries in the time available for gaseous exchange between these two systems.

Thus, the diffusion velocities of di-ethyl ether, ethyl chloride, acetylene and—probably—di-vinyl ether, are sufficiently rapid to permit gaseous equilibrium to be assumed between the anæsthetic content of alveolar air and blood flowing in the pulmonary capillaries; but the solubility of these anæsthetics in circulating blood, relative to the mass of anæsthetic carried to alveolar air per unit time, is such that their partial pressure in alveolar air is very materially reduced by their solution in blood flowing in the pulmonary capillaries. In each instance therefore, *the assumption of gaseous equilibrium between alveolar air and the anæsthetic atmosphere is delayed*: in the case of acetylene slightly, in the case of ethyl chloride moderately, and in the case of di-ethyl ether very considerably. Until gaseous equilibrium has been achieved between these two systems, *the tension of these anæsthetics in blood leaving the pulmonary capillaries is lower than its partial pressure in the anæsthetic atmosphere to which the body is exposed.*

The solubility of the common clinical inhalation anæsthetics in whole blood at body temperature, and their diffusion velocities through the respiratory membrane, are the factors mainly responsible for differences in behaviour during the first sequence of their absorption by the body; their behaviour during this sequence permits them to be divided into the three groups shown in Table 18.

The first group consists of nitrous oxide and ethylene, which are poorly soluble in whole blood at body temperature and whose diffusion velocities through the respiratory membrane are sufficiently rapid. During quiet breathing, anæsthetic equilibrium between alveolar air and an anæsthetic atmosphere containing these two anæsthetics at a constant partial pressure is assumed in about five minutes; because of the rapidity of their diffusion velocity through the respiratory membrane, once anæsthetic equilibrium has been assumed between these two systems the tension of these anæsthetics in blood leaving the pulmonary capillaries equals that of the partial pressure of these anæsthetics in the atmosphere to which the body is exposed. The rate at which anæsthetic equilibrium is assumed between alveolar air and the anæsthetic atmosphere, and in consequence the speed with

anæsthetic required to produce gaseous equilibrium between these two systems.

Suppose, in the conditions postulated above, that a subject is exposed to an anæsthetic atmosphere containing di-ethyl ether at a partial pressure of 100 mm. of mercury. The coefficient of solubility of di-ethyl ether in whole blood at body temperature is 15 c.c., and 450 c.c. of blood require 15 × 450 = 6750 c.c. of di-ethyl ether at 100 mm. of mercury to saturate it to the partial pressure of the anæsthetic in the atmosphere breathed. During quiet breathing, however, only 350 c.c. of di-ethyl ether at 100 mm. of mercury enter alveolar air at each unit respiratory effort; if breathing is the deepest possible, this is increased to 2900 c.c. of di-ethyl ether at 100 mm. of mercury, which is less than half the mass of this anæsthetic necessary to saturate blood to the pressure of di-ethyl ether in the atmosphere breathed. Blood therefore leaves the pulmonary capillaries in gaseous equilibrium with the di-ethyl ether content of alveolar air, but at a di-ethyl ether tension considerably less than its partial pressure in the anæsthetic atmosphere breathed, and the partial pressure of the anæsthetic in alveolar air is very materially reduced by the solution of this mass of di-ethyl ether in circulating blood. This state of affairs will continue until absorption is well advanced. The assumption of equilibrium between alveolar air and the di-ethyl ether anæsthetic atmosphere is therefore slow and does not occur until the body's general absorption of this anæsthetic is well advanced. And the tension of di-ethyl ether, in alveolar air and in blood leaving the pulmonary capillaries, is less than the partial pressure of the anæsthetic in the atmosphere to which the body is exposed throughout the greater part of its absorption.

The behaviour of di-vinyl ether is probably similar to that of di-ethyl ether, and ethyl chloride shows the same trend; for, during quiet breathing the volume of ethyl chloride carried to alveolar air at each unit respiratory effort is about one-third the coefficient of solubility of this anæsthetic in 450 c.c. of whole blood at body temperature. Finally, the coefficient of solubility of acetylene in 450 c.c. of whole blood at body temperature is slightly less than the volume of acetylene carried by effective lung ventilation to alveolar air during quiet breathing.

Thus, the diffusion velocities of di-ethyl ether, ethyl chloride, acetylene and—probably—di-vinyl ether, are sufficiently rapid to permit gaseous equilibrium to be assumed between the anæsthetic content of alveolar air and blood flowing in the pulmonary capillaries; but the solubility of these anæsthetics in circulating blood, relative to the mass of anæsthetic carried to alveolar air per unit time, is such that their partial pressure in alveolar air is very materially reduced by their solution in blood flowing in the pulmonary capillaries. In each instance therefore, *the assumption of gaseous equilibrium between alveolar air and the anæsthetic atmosphere is delayed*: in the case of acetylene slightly, in the case of ethyl chloride moderately, and in the case of di-ethyl ether very considerably. Until gaseous equilibrium has been achieved between these two systems, *the tension of these anæsthetics in blood leaving the pulmonary capillaries is lower than its partial pressure in the anæsthetic atmosphere to which the body is exposed.*

The solubility of the common clinical inhalation anæsthetics in whole blood at body temperature, and their diffusion velocities through the respiratory membrane, are the factors mainly responsible for differences in behaviour during the first sequence of their absorption by the body; their behaviour during this sequence permits them to be divided into the three groups shown in Table 18.

The first group consists of nitrous oxide and ethylene, which are poorly soluble in whole blood at body temperature and whose diffusion velocities through the respiratory membrane are sufficiently rapid. During quiet breathing, anæsthetic equilibrium between alveolar air and an anæsthetic atmosphere containing these two anæsthetics at a constant partial pressure is assumed in about five minutes; because of the rapidity of their diffusion velocity through the respiratory membrane, once anæsthetic equilibrium has been assumed between these two systems the tension of these anæsthetics in blood leaving the pulmonary capillaries equals that of the partial pressure of these anæsthetics in the atmosphere to which the body is exposed. The rate at which anæsthetic equilibrium is assumed between alveolar air and the anæsthetic atmosphere, and in consequence the speed with

TABLE 18.

THE RELATION OF THE DIFFUSION VELOCITY AND THE SOLUBILITY OF INHALATION ANÆSTHETICS UPON THEIR UPTAKE BY CIRCULATING BLOOD.

Anæsthetic	Coefficient of Solubility in 450 c c of Blood at 37°C.	Effective Lung Ventilation of—	Diffusion Velocity	Tension of the Anæsthetic in—
Nitrous oxide Ethylene	185·4 c c. 53 1 c c.	350 c c 350 c.c.	Adequate	Blood, Alveolar air and Anæsthetic atmosphere, equal soon after absorption commences.
Chloroform Cyclopropane Trichlorethylene	*6 39 c c* 5·175 c.c. —	*350 c c.* 350 c c. 350 c.c	Slow	*Alveolar air and Anæsthetic* atmosphere equal soon after absorption commences; Blood always less than alveolar air.
Di-ethyl ether Di-vinyl ether Ethyl chloride Acetylene	*6750* c.c. — 1125·5 c.c. 333 5 c.c.	350 c.c. 350 c c. 350 c c. 350 c.c.	Rapid	*Blood and Alveolar air equal* but less than that of Anæsthetic atmosphere for a great part of absorption.

which blood leaving the pulmonary capillaries reaches a state of equilibrium with the anæsthetic atmosphere, can be materially hastened by the use of carbon dioxide in inspired air. But carbon dioxide, as a means of increasing the rate at which blood leaving the pulmonary capillaries reaches a state of anæsthetic equilibrium with the anæsthetic atmosphere, reaches the limit of its usefulness when anæsthetic equilibrium has been obtained between alveolar air and the anæsthetic atmosphere of constant composition: from this time onwards in the absorption of these anæsthetics, the effect of carbon dioxide is merely to exhaust the subject.

The second group consists of chloroform, cyclopropane, and trichlorethylene, which are relatively insoluble in whole blood and whose diffusion velocities through the respiratory membrane are too slow to permit gaseous equilibrium to be assumed between the anæsthetic content of alveolar air and blood flowing in the pulmonary capillaries in the time available for gaseous exchange. Anæsthetic equilibrium, between alveolar air and an anæsthetic atmosphere containing any one of these three anæsthetics at a constant partial pressure, is rapidly assumed; for the mass of these anæsthetics lost from alveolar air to circulating blood per unit time is so small that it does not significantly reduce their partial pressure in alveolar air. Slow diffusion velocity through the respiratory membrane, however, prevents the assumption of gaseous equilibrium between alveolar air and blood flowing in the pulmonary capillaries in the time available for gaseous exchange between these two systems, and the tension of these anæsthetics in blood leaving the pulmonary capillaries throughout the whole of their absorption is some value less than unity of their partial pressure in alveolar air and, in turn, in the anæsthetic atmosphere to which the body is exposed. Because of the early assumption of gaseous equilibrium between alveolar air and the anæsthetic atmosphere, the use of carbon dioxide during anæsthetic induction to hasten the absorption of these anæsthetics is neither necessary nor desirable. For this reason, too, an increase in the partial pressure of these anæsthetics in the anæsthetic atmosphere is immediately followed by a corresponding increase in the mass of anæsthetic dissolved in blood leaving the pulmonary capillaries. As will be seen later, such a sudden increase in

the blood concentration of one at least of these anæsthetics—chloroform—may be dangerous if not fatal.

The third group consists of di-ethyl ether, di-vinyl ether, ethyl chloride and acetylene, which are highly soluble in whole blood, and whose diffusion velocities through the respiratory membrane are more rapid even than that of carbon dioxide. Anæsthetic equilibrium between alveolar air and blood flowing in the pulmonary capillaries is readily achieved with these anæsthetics in the time available for gaseous exchange. The mass of these anæsthetics absorbed by and dissolved in circulating blood per unit time, relative to the mass which can be carried to alveolar air per unit time, is so large, however, that the anæsthetic content of alveolar air is very materially reduced by the loss of anæsthetic to circulating blood. Consequently, the assumption of anæsthetic equilibrium between alveolar air and the anæsthetic atmosphere is delayed and is achieved at a rate which depends on the solubility of the particular anæsthetic of this group in whole blood. This phenomenon is most pronounced in the case of di-ethyl ether whose coefficient of solubility in whole blood is larger than that of any of the anæsthetics cited in Table 17: anæsthetic equilibrium between the anæsthetic atmosphere and alveolar air and in turn blood flowing in the pulmonary capillaries is achieved most slowly with this anæsthetic. Because of this, the use of carbon dioxide to increase the rate at which blood leaving the pulmonary capillaries reaches a state of anæsthetic equilibrium with a di-ethyl ether anæsthetic atmosphere reaches the limit of its usefulness very late in the absorption of this anæsthetic. Haggard (1927) observed that the absorption and elimination of di-ethyl ether varied " practically, proportionally with the volume of [effective] lung ventilation," while the absorption or elimination of less soluble gases such as ethylene, was very slightly affected by variations in the volume of effective lung ventilation. In the absence of the relevant data, it is assumed that di-vinyl ether behaves in a manner similar to that of di-ethyl ether. Ethyl chloride has a solubility in whole blood about one-sixth that of di-ethyl ether; but relative to the other anæsthetics in common clinical use, its solubility is high, while acetylene has the lowest solubility of the members of this group. In each instance, an increase of

the carbon dioxide content of inspired air will materially hasten the assumption of gaseous equilibrium between alveolar air and an anæsthetic atmosphere containing ethyl chloride or acetylene: until anæsthetic equilibrium has been assumed between these two systems, the use of carbon dioxide to hasten absorption has a rational and a useful place in anæsthetic induction with these anæsthetics. The field of its usefulness is greatest in di-ethyl ether anæsthesia; decreasing as the solubility of the members of this group in whole blood diminishes, it is least in acetylene anæsthesia.

THE THIRD PHASE of the absorption of inhalation anæsthetics by the body is constituted by the mass movement of these gases and vapours dissolved in circulating blood, from the pulmonary capillaries to the capillaries of the tissue cells of the body.

Haldane (1935) estimated that the total weight of blood in the body of a 70-kilo man is about 6·5% of his body weight—equivalent to about 4½ litres; he further calculated that the circulatory rate in resting conditions is 8·5 - 8·8 litres per minute. For the purpose of this discussion it is assumed that the total blood volume is 4½ litres and that the circulatory rate is uniform at 9 litres per minute. The term " a round of blood " is used by Haldane to mean the passage of 4500 c.c. of blood from the pulmonary capillaries, through the systemic and venous circulatory system, and back to the pulmonary capillaries. It can be said that the whole volume of blood makes one round or passage of the circulatory system every 30 seconds (circa).

With these standards, it is a simple matter to calculate the volume of a given inhalation anæsthetic at a given pressure, dissolved in 4500 c c. of whole blood. It is termed the *absorptive capacity of one round of blood*. Thus, the coefficient of solubility of nitrous oxide in whole blood at 37°C. is 0·412 c.c. and 4500 c.c. of blood therefore dissolves 0 412 × 4500 = 1854 c.c. of nitrous oxide when saturated to the pressure of nitrous oxide in contact with this blood. The nitrous oxide absorptive capacity of one round of blood at any given pressure is therefore 1854 c.c., and the mass of nitrous oxide varies as its pressure. When the partial pressure of nitrous oxide is 600 mm of mercury, its tension in solution is 600 mm. of mercury and 1854 of nitrous oxide at 600 mm. of mercury weighs 2 525 gm. If the partial pressure of nitrous

the blood concentration of one at least of these anæsthetics—chloroform—may be dangerous if not fatal.

The third group consists of di-ethyl ether, di-vinyl ether, ethyl chloride and acetylene, which are highly soluble in whole blood, and whose diffusion velocities through the respiratory membrane are more rapid even than that of carbon dioxide. Anæsthetic equilibrium between alveolar air and blood flowing in the pulmonary capillaries is readily achieved with these anæsthetics in the time available for gaseous exchange. The mass of these anæsthetics absorbed by and dissolved in circulating blood per unit time, relative to the mass which can be carried to alveolar air per unit time, is so large, however, that the anæsthetic content of alveolar air is very materially reduced by the loss of anæsthetic to circulating blood. Consequently, the assumption of anæsthetic equilibrium between alveolar air and the anæsthetic atmosphere is delayed and is achieved at a rate which depends on the solubility of the particular anæsthetic of this group in whole blood. This phenomenon is most pronounced in the case of di-ethyl ether whose coefficient of solubility in whole blood is larger than that of any of the anæsthetics cited in Table 17: anæsthetic equilibrium between the anæsthetic atmosphere and alveolar air and in turn blood flowing in the pulmonary capillaries is achieved most slowly with this anæsthetic. Because of this, the use of carbon dioxide to increase the rate at which blood leaving the pulmonary capillaries reaches a state of anæsthetic equilibrium with a di-ethyl ether anæsthetic atmosphere reaches the limit of its usefulness very late in the absorption of this anæsthetic. Haggard (1927) observed that the absorption and elimination of di-ethyl ether varied " practically, proportionally with the volume of [effective] lung ventilation," while the absorption or elimination of less soluble gases such as ethylene, was very slightly affected by variations in the volume of effective lung ventilation. In the absence of the relevant data, it is assumed that di-vinyl ether behaves in a manner similar to that of di-ethyl ether. Ethyl chloride has a solubility in whole blood about one-sixth that of di-ethyl ether, but relative to the other anæsthetics in common clinical use, its solubility is high, while acetylene has the lowest solubility of the members of this group In each instance, an increase of

oxide is halved, the mass of this gas in solution is halved, for 1854 c.c. of nitrous oxide at 300 mm. of mercury weighs 1·2612 gm.

Table 19 shows the absorptive capacity of one round of blood at 37°C. calculated in this fashion for the inhalation anæsthetics in common clinical use. If anæsthetic equilibrium was always assumed between blood leaving the pulmonary capillaries and the anæsthetic atmosphere to which the body is exposed, the absorptive capacity of one round of blood would represent the mass of the given anæsthetic carried from the pulmonary capillaries to the tissue capillaries every 30 seconds. But, it should be noted, the behaviour of inhalation anæsthetics in the first sequence of absorption is such that the absorptive capacity of one round of blood does not always coincide with *the mass of inhalation anæsthetic actually carried in each round of blood.*

Once anæsthetic equilibrium has been assumed between the anæsthetic atmosphere and alveolar air, it has been seen that blood leaving the pulmonary capillaries is saturated with nitrous oxide or ethylene to the partial pressure of these gases in the anæsthetic atmosphere to which the body is exposed: and the *carrying capacity of one round of blood* for nitrous oxide and ethylene is equal to the absorptive capacity of 4500 c.c. of blood for these gases.

The carrying capacity of one round of blood for chloroform, cyclopropane, and trichlorethylene, however, is less than the absorptive capacity of 4500 c.c. of blood for these anæsthetics, for their slow diffusion velocities through the respiratory membrane prevent the assumption of anæsthetic equilibrium, between the anæsthetic atmosphere and blood leaving the pulmonary capillaries, in the time available for gaseous exchange between these two systems. The *carrying capacity of one round of blood* for these three anæsthetics is therefore some power less than unity of their absorptive capacity in 4500 cc. of blood.

Because the absorptive capacity of 4500 c.c. of blood for di-ethyl ether, ethyl chloride, acetylene and—probably—di-vinyl ether is so large, relative to the mass of these anæsthetics in alveolar air available for solution in circulating blood, the carrying capacity of one round of blood for these four anæsthetics is less

TABLE 19.

THE RELATION OF THE ABSORPTIVE CAPACITY TO THE CARRYING CAPACITY OF ONE ROUND OF BLOOD.

Anæsthetic	Absorptive Capacity of One Round of Blood at 37°C.	Percentage Saturation to partial pressure of Anæsthetic	Carrying Capacity of one Round of Blood
Nitrous oxide	1,854 c.c.	100%	1,854 c.c
Ethylene	531 c.c.		531 c.c.
Chloroform	63 9 c.c.	Less than 100% throughout absorption	Less than the absorptive capacity throughout the whole of absorption
Cyclopropane	51 75 c.c.		
Trichlorethylene	—		
Di-ethyl ether	67,500 c.c.	Less than 100% *until absorption* is well advanced	Less than the absorptive capacity until absorption is well advanced
Di-vinyl ether	—		
Ethyl chloride	11,255 c.c.		
Acetylene	3,334 5 c.c.		

70 kilos will take up . . . . about 70% more nitrogen than an equal weight of blood would take up." These opinions conflict: nitrogen, for instance, has an oil/water partition coefficient of 5·3. Haldane's view of the influence of fatty tissue on the uptake of nitrogen by the body taken as a whole coincides with the conclusions reached on the uptake of narcotics by living cells, which was held to be a differential solubility process depending in the main upon the water and lipoid content of the cells. The greater solubility of inhalation anæsthetics with an oil/water partition coefficient of 3·4 and more, in whole blood relative to their solubility in water or in plasma, emphasises the influence of the lipoid content of erythrocytes and suggests that the 12% of fat and fat-like substances contained in Man's body can be expected to exert a similar and a correspondingly greater influence upon the absorptive capacity of the body for anæsthetic gases and vapours.

In the absence of experimental observations, it seems justifiable therefore to use terms of the water and lipoid content of the body in estimating the absorptive capacity of the body, taken as a whole, for the anæsthetic gases and vapours.

, Thus:

The body of a 70-kilo man contains about 80% (56,000 grams) of water and about 12% (8400 grams) of fat. Since the coefficient of solubility of nitrous oxide in water is 0·395 c.c., the water content of his body dissolves

$$56{,}000 \times 0\ 395 = 22{,}120 \text{ c.c. (circa) of nitrous oxide}$$

Nitrous oxide is 3·4 times more soluble in olive oil than in water and if its solubility in olive oil (viz. 0 395 × 3·4) is taken as a measure of its solubility in body fats, then his body fats dissolve

$$8{,}400 \times (0\ 395 \times 3\ 4) = 11{,}281 \text{ c.c. (circa) of nitrous oxide}$$

And if body tissues other than water and fats are ignored, the body of this 70-kilo man has an absorptive capacity for nitrous oxide of about

$$22{,}120 + 11{,}281 = 33{,}401 \text{ c.c. (circa) of nitrous oxide.}$$

The absorptive capacity of the body of a 70-kilo man for the inhalation anæsthetics in common clinical use, estimated in this fashion, is shown in Table 20. These figures are without doubt approximations, but there is so little difference between the

than the absorptive capacity of 4500 c.c. of blood throughout the greater part of their absorption by the body. The *carrying capacity of one round of blood* for di-ethyl ether, di-vinyl ether, ethyl chloride and acetylene is therefore some power less than unity of the partial pressure of these anæsthetics in the anæsthetic atmosphere, until anæsthetic equilibrium has been assumed between this atmosphere and alveolar air.

THE FOURTH PHASE of the absorption of inhalation anæsthetics by the body is constituted by the diffusion of these gases and vapours from blood in the tissue capillaries via extracellular fluid to the tissue cells and by their ultimate solution in the cells themselves. It is a diffusion and solution phase in which the diffusion of the anæsthetic gas or vapour to the region of lower pressure, the cell, is governed by the factors seen to apply in the uptake of narcotics by living cells. The uptake of an anæsthetic by any of the cells of Man's body is a differential solubility process, identical in every respect with the uptake of narcotics by unicellular organisms from the extracellular fluid in which they are immersed. The absorption of an anæsthetic is complete when the volume of the anæsthetic dissolved in the cells of the whole body has raised the tension of the anæsthetic in solution in these cells to that of the partial pressure of the anæsthetic in the atmosphere to which the body is exposed. The volume of a particular anæsthetic which must be dissolved in the cells of the whole body to produce this state of equilibrium has been termed, for the purpose of this discussion, *the absorptive capacity of the body for that gas or vapour.* It is, in effect, the coefficient of solubility of the anæsthetic in the body taken as a whole.

Little information is available regarding the absorptive capacity of Man's body for the inhalation anæsthetics in common clinical use. Henderson and Haggard (1927) state. "With most gases the average [solubility] for the body taken as a whole is probably nearly the same as the solubility in blood. This is true at least for those gases and vapours which have been chiefly studied in this relation; for example, ethyl ether, hydrogen and nitrogen." On the other hand, Haldane (1935) states: "Taking into consideration the amount of fatty material in the body, Boycott, Damant and Haldane estimated that the whole body of a man weighing

carrying capacity of one round of blood. Let it be exactly 18 times the carrying capacity of one round of blood, viz. 1,854 × 18 = 33,372 c.c. of nitrous oxide at 600 mm. of mercury. It follows, when anæsthetic equilibrium has been assumed between the nitrous oxide pressure of the anæsthetic atmosphere and alveolar air, that the blood carries by mass movement to the tissue capillaries every 30 seconds, one-eighteenth part of the mass of nitrous oxido required to fully saturate the body to the partial pressure of nitrous oxide in the atmosphere breathed.

Suppose the body of a 70-kilo man at the uniform respiratory and circulatory rate specified above is exposed to an anæsthetic atmosphere containing nitrous oxide at a partial pressure of 600 mm. of mercury and oxygen at a partial pressure of 160 mm. of mercury, and suppose for simplicity of description that alveolar air was immediately saturated with nitrous oxide to its partial pressure in the anæsthetic atmosphere.

Under these conditions during the first 30 seconds after exposure to this atmosphere, one round of blood is saturated with nitrous oxide to its partial pressure in the anæsthetic atmosphere; and during this 30 seconds this first round of blood carries to the tissue capillaries 1,854 c.c. of nitrous oxide at 600 mm. of mercury, or one-eighteenth part of the mass of nitrous oxide required to saturate the whole body to 600 mm. of mercury. This mass of nitrous oxide is redistributed by diffusion and solution, *via* extracellular fluid, between blood, tissue fluids and the tissue cells during the first 30 seconds; when it has diffused to fill its new volume of 33,372 c.c.—which is the absorptive capacity of the body *for nitrous oxide—its average tension in solution in blood*, the tissue fluids, and the tissue cells is 33 3 mm. of mercury, for:

$$p' \times 33{,}372 = 1854 \times 600 \text{ (Boyle's Law)}$$
$$\text{and } p' = 33\ 3 \text{ mm. of Hg.}$$

During this first 30 seconds after exposure to this atmosphere, the body has absorbed one-eighteenth part of the mass of nitrous oxide required to saturate it to the partial pressure of nitrous oxide in the anæsthetic atmosphere and seventeen-eighteenths of the absorptive capacity of the body remains to be absorbed before the body is saturated with nitrous oxide at 600 mm. of mercury.

At the end of the first 30 seconds, the average tension of nitrous

absorptive capacity of the body for nitrogen, calculated in this fashion, viz. 1276 c.c., and Haldane's figure for a 70-kilo man, viz. 1287 c.c. at 600 mm. of mercury or about one litre at N.T.P., that the values for this index given in Table 20 may be employed with advantage to compare and contrast the rate and character of the absorption of these anæsthetics by the body taken as a whole

TABLE 20.

THE ABSORPTIVE CAPACITY OF THE WHOLE BODY FOR THE ANÆSTHETICS IN COMMON CLINICAL USE.

Anæsthetic	Absorptive Capacity of a 70-kilo man (estimated)
Nitrous oxide	33,401 c.c.
Ethylene	12,059 c.c.
Chloroform	2,352 c.c.
Cyclopropane	2,153 c.c.
Trichlorethylene	—
Di-ethyl ether	1,164,447 c.c.
Di-vinyl ether	—
Ethyl chloride	—
Acetylene	53,403 c.c.
Nitrogen	1,276 c.c. (estimated) 1,287 c.c. (Haldane)

The rate and character of the absorption of a given inhalation anæsthetic by the body taken as a whole *is determined by the ratio of the carrying capacity of one round of blood to the absorptive capacity of the body taken as a whole for this anæsthetic.*

Exposed to an anæsthetic atmosphere containing nitrous oxide at a partial pressure of 600 mm of mercury, the carrying capacity of one round of blood is 1,854 c.c. of nitrous oxide at 600 mm. of mercury, and the estimated absorptive capacity of the body taken as a whole is 33,401 c.c. of nitrous oxide at 600 mm. of mercury. The estimated absorptive capacity of the body for nitrous oxide is thus about 18 times greater than the nitrous oxide

part of the mass of nitrous oxide now required to saturate the body, viz. 1653·8 c.c. of nitrous oxide at 600 mm. of mercury. When this mass of nitrous oxide has been carried to the tissue capillaries and redistributed by diffusion between blood, tissue fluids and tissue cells, the total mass of nitrous oxide absorbed by the body is 1854 + 1751 + 1653·8 = 5258·8 c.c. of nitrous oxide at 600 mm. of mercury, and its average tension in solution in the body is 94·5 mm. of mercury, for:

$$p' \times 33{,}372 = 5258{\cdot}8 \times 600$$
$$\text{and } p' = 94{\cdot}5 \text{ mm. of Hg.}$$

Thus, as absorption proceeds, each successive round of blood carries to the tissue capillaries, by mass movement, 1854 c.c. of nitrous oxide at 600 mm. of mercury. Because of the progressive rise of the nitrous oxide tension in the body and in turn in mixed venous blood returning to the pulmonary capillaries, the mass of nitrous oxide absorbed into circulating blood to produce gaseous equilibrium between this solvent and alveolar air becomes with each successive round of blood progressively smaller—it amounts to one-eighteenth part of the mass of nitrous oxide then required to produce full saturation—and if a is the absorptive capacity of the body for nitrous oxide, the mass of this gas absorbed at each successive round of blood is represented thus:

$$[1/18\text{th of } a] + [1/18\text{th of } 17/18\text{th of } a] + [1/18\text{th of } (17/18)^2 \text{ of } a]$$
and so on.

(where a equals 33372 c.c. of nitrous oxide at 600 mm. of Hg.)

Figure 8 represents the time-concentration curve of the absorption of nitrous oxide by the body in the conditions specified, and Table 21 the data from which this curve is constructed. Together they illustrate the rate and character of the absorption of nitrous oxide by the body of a 70-kilo man. It is seen that the body is 25% saturated in 2½ minutes, 50% saturated in 6 minutes, and 75% saturated in 12 minutes; the last 25% saturation is very slow, and full saturation occurs in infinite time. Thus, after 20 minutes' absorption, the body is 90% saturated, after 32 minutes' absorption about 97% saturated; but after 50 minutes the degree of saturation has reached only 99.2%. Full saturation, in fact, can be achieved only by the use of overpressure. (cf. page 159.)

oxide in solution in the body is 33·3 mm. of mercury, and 4500 c.c. of mixed venous blood returns to the lungs containing 1854 c.c. of nitrous oxide with a tension in solution of 33·3 mm. of mercury. Re-entering the pulmonary capillaries, this 4500 c.c. of blood again become saturated with nitrous oxide at its partial pressure in alveolar air, viz. 600 mm. of mercury. To achieve this it must dissolve 1854 c.c. of nitrous oxide at (600−33·3) = 566 7 of mercury or 1751 c.c. of nitrous oxide at 600 mm. of mercury. This is one-eighteenth part of the mass of nitrous oxide now required to saturate the body, or one-eighteenth of seventeen-eighteenths of the absorptive capacity of the body for nitrous oxide. The second round of blood therefore sets out on its second round of the circulatory system containing 1854 c.c. of nitrous oxide at 600 mm. of mercury; and of this, 1751 c.c. of nitrous oxide at 600 mm. of mercury diffuse from the tissue capillaries *via* extracellular fluid to dissolve in the tissue cells. At the end of this second round of blood the total mass of nitrous oxide absorbed by the body is 1854 + 1751 = 3605 c.c. of nitrous oxide at 600 mm. of mercury; when this mass of nitrous oxide has been distributed between blood, tissue fluids, and tissue cells, its average tension in solution in the body is 64·8 mm. of mercury for:

$$p' \times 33{,}372 = 3605 \times 600$$
$$\text{and } p' = 64\ 8 \text{ mm of Hg}$$

During this second round of blood, the body has absorbed one-eighteenth part of seventeen-eighteenths of the absorptive capacity of the body for nitrous oxide and at the end of this second round of blood the total mass of nitrous oxide absorbed is $\frac{1}{18} + (\frac{1}{18} \times \frac{17}{18})$ of the absorptive capacity of the body for this gas, and $(17/18\text{th})^2$ of the absorptive capacity of the body for nitrous oxide remains to be absorbed to produce full saturation

At the end of this second round of blood, after one minute's absorption, the average tension of nitrous oxide in the body is 64 8 mm. of mercury, and 4500 c c. of mixed venous blood return to the pulmonary capillaries containing 1854 c.c. of nitrous oxide with a tension in solution of 64·8 mm of mercury It is again saturated with nitrous oxide at its partial pressure in alveolar air, viz. 600 mm. of mercury, and to achieve this, must dissolve one-eighteenth

part of the mass of nitrous oxide now required to saturate the body, viz. 1653·8 c.c. of nitrous oxide at 600 mm. of mercury. When this mass of nitrous oxide has been carried to the tissue capillaries and redistributed by diffusion between blood, tissue fluids and tissue cells, the total mass of nitrous oxide absorbed by the body is 1854 + 1751 + 1653 8 = 5258·8 c.c. of nitrous oxide at 600 mm. of mercury, and its average tension in solution in the body is 94·5 mm. of mercury, for:

$$p' \times 33{,}372 = 5258.8 \times 600$$
$$\text{and } p' = 94.5 \text{ mm. of Hg}$$

Thus, as absorption proceeds, each successive round of blood carries to the tissue capillaries, by mass movement, 1854 c.c. of nitrous oxide at 600 mm. of mercury. Because of the progressive rise of the nitrous oxide tension in the body and in turn in mixed venous blood returning to the pulmonary capillaries, the mass of nitrous oxide absorbed into circulating blood to produce gaseous equilibrium between this solvent and alveolar air becomes with each successive round of blood progressively smaller—it amounts to one-eighteenth part of the mass of nitrous oxide then required to produce full saturation—and if *a* is the absorptive capacity of the body for nitrous oxide, the mass of this gas absorbed at each successive round of blood is represented thus:

$$[1/18\text{th of } a] + [1/18\text{th of } 17/18\text{th of } a] + [1/18\text{th of } (17/18)^2 \text{ of } a]$$
and so on.

(where *a* equals 33372 c c. of nitrous oxide at 600 mm. of Hg.)

Figure 8 represents the time-concentration curve of the absorption of nitrous oxide by the body in the conditions specified, and Table 21 the data from which this curve is constructed. Together they illustrate the rate and character of the absorption of nitrous oxide by the body of a 70-kilo man. It is seen that the body is 25% saturated in 2½ minutes, 50% saturated in 6 minutes, and 75% saturated in 12 minutes; the last 25% saturation is very slow, and full saturation occurs in infinite time. Thus, after 20 minutes' absorption, the body is 90% saturated, after 32 minutes' absorption about 97% saturated; but after 50 minutes the degree of saturation has reached only 99.2%. Full saturation, in fact, can be achieved only by the use of overpressure. (*cf.* page 159.)

TABLE 21.

The Absorption of Nitrous Oxide at 600 mm. of Hg. by a 70-Kilo man, at a uniform respiratory and circulatory rate

(Assuming the immediate assumption of gaseous equilibrium between the anæsthetic atmosphere and alveolar air.)

Rounds of Blood	Duration of absorption (Minutes)	Volume at 600 mm of Hg. absorbed per round of blood (c.c)	Total volume at 600 mm. of Hg. absorbed after each round. (c c.)	Saturation (%)	Average tension in the body after each round. (Mm. of Hg.)
1		1854	1854		33·3
2	1	1751	3605		64·8
3		1653·8	5258 8		94·5
4	2	1560 6	6818		122·7
5	2½	1473 8	8291 8	25	149.2
12	6	1045·2	15562·9	50	279·7
24	12	495·1	24862 6	75	447·1
40	20	197 8	29900·6	90	540 6
61	32	49·9	32410·7	97	582 5
78	39	22·1	32875 2	98 5	591·7
100	50	6·1	33140 8	99 2	596 5

It is clear that the rate and the character of the absorption of nitrous oxide by the body taken as a whole are determined by the ratio of the carrying capacity of one round of blood to the absorptive capacity of the body taken as a whole, for this anæsthetic. For the purpose of discussion, this ratio is termed the

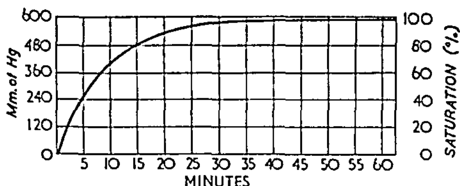


FIGURE 8.

The rate of saturation of the body with nitrous oxide (constructed from figures in Table 16).

Absorption Coefficient of the body for the particular anæsthetic gas or vapour, and it is $\frac{1}{18}$ for nitrous oxide. Table 22 shows that the absorption coefficient for ethylene, to the nearest whole number, is $\frac{1}{23}$. The rate of absorption of ethylene by the body is consequently slower than that of nitrous oxide. It is clear, too, that the absorption of nitrous oxide by the body taken as a whole is exponential in character, and that the amount absorbed decreases *progressively in a logarithmic manner* as absorption proceeds. This is attributed to the mass movement per unit time by circulating blood of a constant fraction—in the case of nitrous oxide one-eighteenth—of the mass of this anæsthetic then required to produce full saturation to the partial pressure of the anæsthetic in the atmosphere to which the body is exposed.

Since the inhalation anæsthetics in common clinical use do not react chemically with one another, with the respiratory gases and vapours, or with the tissue fluids and tissue cells, and because they are not normal tissue substrates and have no tissue utilization rate, the character of their absorption by the body is similar to that of nitrous oxide. Hence if *a* equals the absorptive capacity

of the body for a given inhalation anæsthetic, and $\frac{1}{b}$ equals its absorption coefficient, then the manner of its absorption by the body is as follows:

During the first period of absorption, $\frac{a}{b}$ is absorbed by the body and $(a - \frac{a}{b})$ or $a(1 - \frac{1}{b})$ is still required to produce full saturation of the body.

$\frac{a}{b}(1 - \frac{1}{b})$ is absorbed during the second period and $a(1 - \frac{1}{b})^2$ is then required to produce full saturation of the body.

$\frac{a}{b}(1 - \frac{1}{b})^2$ is absorbed during the third period and $a(1 - \frac{1}{b})^3$ is still required—and so on.

And the mass of a given inhalation anæsthetic absorbed by the body at each successive period of time can be represented thus:

$\frac{a}{b} + \frac{a}{b}(1 - \frac{1}{b}) + \frac{a}{b}(1 - \frac{1}{b})^2 + \frac{a}{b}(1 - \frac{1}{b})^3$ and so on.

This type of mathematical expression gives rise to the curve of logarithmic shape as seen in Figure 8. The absorption of the inhalation anæsthetics in common clinical use is exponential in character.

Once anæsthetic equilibrium has been assumed between alveolar air and an anæsthetic atmosphere of constant composition containing nitrous oxide or ethylene—and in clinical practice this state of equilibrium is attained after about 5 minutes—the estimated absorption coefficient of these anæsthetics (Table 22) can be looked upon as a reasonably accurate index of the rate of absorption of these anæsthetics by the body taken as a whole, for reference to Table 19 shows that the carrying capacity of one round of blood is equal to the absorptive capacity of one round of blood for these inhalation anæsthetics.

Although anæsthetic equilibrium is rapidly assumed between alveolar air and an anæsthetic atmosphere of constant composition containing chloroform, cyclopropane and trichlorethylene, blood leaving the pulmonary capillaries cannot be saturated to the partial pressure of these inhalation anæsthetics in the anæsthetic atmosphere to which the body is exposed, for Table 19 shows that the carrying capacity of one round of blood is *less than* the absorptive capacity of one round of blood for these inhalation anæsthetics. It follows that the estimated absorption coefficient of the body for these anæsthetics, as shown in Table 22, is too high, and that the rate of their absorption by the body taken as a whole is *even*

TABLE 22.

THE ABSORPTION COEFFICIENT OF A 70-KILO MAN.

Anæsthetic	Carrying Capacity of one round of Blood at 37°C.	Absorptive Capacity of a 70-kilo man (estimated)	Absorption Coefficient of a 70-kilo man (estimated)
Nitrous oxide	1,854 c.c.	33,401 c.c.	$\frac{1}{18}$
Ethylene	531 c.c.	12,059 c.c.	$\frac{1}{23}$
Chloroform	$<$ 63·9 c.c.	2,352 c.c.	$< \frac{1}{37}$ (throughout absorption)
Cyclopropane	$<$ 51·75 c.c.	2,153 c.c.	$< \frac{1}{42}$
Trichlorethylene	—	—	—
Di-ethyl ether	$<$ 67,500 c.c.	1,164,447 c.c.	$< \frac{1}{17}$ (until absorption is well advanced)
Di-vinyl ether	—	—	
Ethyl chloride	$<$ 11,250 c.c.	—	
Acetylene	$<$ 3,334·5 c.c.	53,403 c.c.	$< \frac{1}{16}$
Nitrogen	49·5 c.c.	1,276 c.c. (*estimated*) 1,287 c.c. (*Haldane*)	$\frac{1}{26}$ $\frac{1}{26}$

slower than the estimated absorption coefficient indicates. It is clear too that the tension of these anæsthetics in solution in the body when their uptake by the body from an atmosphere of constant composition has ceased, can never equal that of the partial pressure of these anæsthetics in this atmosphere—which accounts for Tissot's inability to achieve full saturation in dogs exposed to chloroform at a constant partial pressure even after 8 hours' exposure.

Table 19 shows that the absorptive capacity of one round of blood for di-ethyl ether, ethyl chloride, acetylene and probably di-vinyl ether is so much in excess of the mass of these anæsthetics available for solution in alveolar air, throughout part at least of their absorption, that the mass of these anæsthetics carried to the tissues in one round of blood is *less than* the absorptive capacity of one round of blood for these anæsthetics and *will remain so until anæsthetic equilibrium has been assumed between alveolar air and an anæsthetic atmosphere containing these anæsthetics at a constant partial pressure.* Consequently, their estimated absorption coefficient shown in Table 22 is too high throughout part at least of their absorption. The disparity is greatest in the case of di-ethyl ether and it decreases as the solubility of these anæsthetics in whole blood diminishes, to be least in the case of acetylene.

Control of Rate of Absorption. The rate of absorption of a given inhalation anæsthetic by the body taken as a whole may be increased in two ways.

If a subject is exposed to an anæsthetic atmosphere of constant composition, the rate of absorption of an inhalation anæsthetic can be wittingly hastened only by variations in the volume of effective lung ventilation. An increase in the volume of effective lung ventilation hastens the assumption of anæsthetic equilibrium between alveolar air and the anæsthetic atmosphere and in this manner increases the rate of absorption of the inhalation anæsthetic by the body taken as a whole. With anæsthetics such as nitrous oxide, ethylene, chloroform, cyclopropane and trichlorethylene, the use of carbon dioxide in inspired air has a limited value, for anæsthetic equilibrium is assumed between alveolar air and the anæsthetic atmosphere in a relatively short period of time because

of the low solubility of these anæsthetics in whole blood. With anæsthetics such as di-ethyl ether, di-vinyl ether, ethyl chloride and acetylene whose solubility in whole blood is large, the use of carbon dioxide in inspired air to hasten absorption has a wider

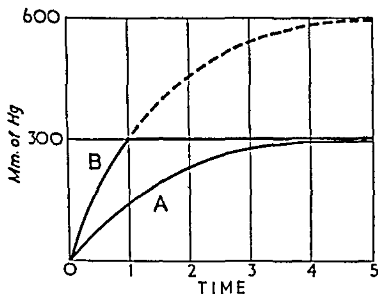


FIGURE 9.

The effect of overpressure on the rate of absorption of inhalation anæsthetics.

influence, which lasts—in the case of the most soluble of these anæsthetics, di-ethyl ether—until absorption is well advanced. The circulatory rate, however, cannot be influenced in a controllable manner in the interests of rapid absorption.

Because the absorption of inhalation anæsthetics by the body taken as a whole is exponential in character, the absorption of an inhalation anæsthetic to a given tension in solution in the body may be hastened by the use of *overpressure*. Suppose it is required to saturate the body with an inhalation anæsthetic to 300 mm. of mercury. This may be achieved in two ways. The body may be exposed to an anæsthetic atmosphere containing this anæsthetic at a pressure of 300 mm. of mercury. Curve A of Figure 9 shows that in this instance, anæsthetic equilibrium is achieved between this atmosphere and the body taken as a whole, in about 5 units of time. If, however, the body is exposed to an

atmosphere containing this anæsthetic at a partial pressure of 600 mm. of mercury, half saturation to this tension is achieved in about one unit of time, and if at this point the pressure of the anæsthetic in the anæsthetic atmosphere is reduced by half to 300 mm. of mercury, then the body is in equilibrium with the anæsthetic atmosphere. By the use of overpressure, it has been saturated with the anæsthetic to 300 mm. of mercury, in about one-fifth of the time previously required.

It can be concluded that the absorption of inhalation anæsthetics by the body taken as a whole is exponential in character and that each inhalation anæsthetic is absorbed at a rate determined by its physical properties and the exponential character of its absorption. These characteristics of the particular inhalation anæsthetic are conveniently expressed as the absorption coefficient of the given anæsthetic for the body taken as a whole, this index, shown in Table 22, indicates the rate of absorption of the inhalation anæsthetics in common clinical use.[1] The characteristic rate of absorption of a given inhalation anæsthetic may be modified in an upward and a downward direction by alterations in the volume of effective lung ventilation. Deep breathing hastens, and shallow breathing retards, the characteristic rate of absorption of a given inhalation anæsthetic; but alterations in the volume of effective lung ventilation reaches the limit of usefulness in this respect when anæsthetic equilibrium has been achieved between the anæsthetic atmosphere and alveolar air.

[1] It is to be emphasised that the rate of absorption of an inhalation anæsthetic atmosphere of constant composition and the uptake of. an effective concentration of a given anæsthetic by specific areas of functional activity of the brain are not synonymous terms.

References

1 Adriani, J (1946) "The Chemistry of Anæsthesia," p 165. Blackwell Scientific Publications, Oxford
2. Boycott, A E, Damant, G C C, and Haldane, J. S (1908) *J. Hyg Camb.* 8, 302
3. Embling, E H (1906) *Proc roy Soc B* 78, 392.
4. Evans, Miss S (1945) Personal communication.
5. Haggard, H. W. (1924) *J biol. Chem.* 59, 753
6. Haldane, J. S, and Priestley, J. G (1935) "Respiration" p 339 Clarendon Press, Oxford.
7. Henderson, Y, and Haggard, H W (1927) "Noxious Gases" p. 73. The Chemical Catalog Co., New York.
8. Keith, A (1909) Quoted from "Further Advances in Physiology." p. 199. Edward Arnold, London

9. Kochmann, M. (1936). "Handbuch der Experimentellen Pharmakologie, Zweiter band." p. 29. Julius Springer, Berlin.
10. Leake, C. D., and Chen, M. Y. (1930). *Proc. Soc. exp. Biol. N.Y.* 28, 151.
11. Nicloux, M. et Al (1934). *C. R. Soc. Biol. Paris.* 115, 1284.
12. Orcutt, F. S., and Waters, R. M. (1933). "Anesth. & Analges." 12, 45.
13. Schoen, R. (1923). *Hoppe-Seyl. Z.* 127, 243.
14 Siebeck, R. A., (1909). *Skand. Arch. Physiol.* 21, 378.
15. Winterstein, H. (1926). *Die Narkose.* Julius Springer, Berlin.

atmosphere containing this anæsthetic at a partial pressure of 600 mm. of mercury, half saturation to this tension is achieved in about one unit of time, and if at this point the pressure of the anæsthetic in the anæsthetic atmosphere is reduced by half to 300 mm. of mercury, then the body is in equilibrium with the anæsthetic atmosphere. By the use of overpressure, it has been saturated with the anæsthetic to 300 mm. of mercury, in about one-fifth of the time previously required.

It can be concluded that the absorption of inhalation anæsthetics by the body taken as a whole is exponential in character and that each inhalation anæsthetic is absorbed at a rate determined by its physical properties and the exponential character of its absorption. These characteristics of the particular inhalation anæsthetic are conveniently expressed as the absorption coefficient of the given anæsthetic for the body taken as a whole, this index, shown in Table 22, indicates the rate of absorption of the inhalation anæsthetics in common clinical use.[1] The characteristic rate of absorption of a given inhalation anæsthetic may be modified in an upward and a downward direction by alterations in the volume of effective lung ventilation. Deep breathing hastens, and shallow breathing retards, the characteristic rate of absorption of a given inhalation anæsthetic; but alterations in the volume of effective lung ventilation reaches the limit of usefulness in this respect when anæsthetic equilibrium has been achieved between the anæsthetic atmosphere and alveolar air.

[1] It is to be emphasised that the rate of absorption of an inhalation anæsthetic atmosphere of constant composition and the uptake of an effective concentration of a given anæsthetic by specific areas of functional activity of the brain are not synonymous terms.

References.

1 Adriani, J. (1946) "The Chemistry of Anæsthesia," p. 165 Blackwell Scientific Publications, Oxford.
2. Boycott, A E, Damant, G C. C., and Haldane, J. S. (1908). *J. Hyg. Camb.* 8, 302
3. Embling, E. H (1906) *Proc. roy. Soc B.* 78, 392.
4. Evans, Miss S (1945) Personal communication
5. Haggard, H. W (1924). *J biol Chem* 59, 753
6. Haldane, J. S., and Priestley, J. G. (1935). "Respiration." p. 339 Clarendon Press, Oxford.
7. Henderson, Y., and Haggard, H. W. (1927). "Noxious Gases." p. 73. The Chemical Catalog Co , New York.
8. Keith, A (1909) Quoted from "Further Advances in Physiology." p. 199 Edward Arnold, London

As in the body taken as a whole, so also in individual types of body tissue, the rate and character of the absorption of a given inhalation anæsthetic by a particular type of body tissue is determined by (a) the absorptive capacity of the tissue for a given anæsthetic, and (b) the share of gas-bearing blood which it receives per round of circulating blood. Exposed to an anæsthetic atmosphere of constant composition, each organ of the body can be expected to achieve gaseous equilibrium with this atmosphere at a rate which depends upon the absorption coefficient of the particular organ for the given inhalation anæsthetic. The character of its absorption by each and every organ of the body is exponential.

The evidence suggests that the absorptive capacity of a particular type of body tissues for a given inhalation anæsthetic depends in the main upon (a) the *lipoid-water content of the particular tissue*, and (b) *the oil/water partition coefficent of the given anæsthetic.*

Leathes (1910) states: " The term fat has a precisely defined chemical meaning which restricts its application to a certain number only of the substances of this group and yet many of these substances that are in the strict chemical sense fats have, on account of their physical properties, to be spoken of as oils. . . . while for a large class, the physiological importance of which is daily coming more into evidence, no better general name has been proposed than ' lipoids,' which is at once a cloak for ignorance and an indefinable limbo into which anyone can thrust anything of which he knows little or nothing." Maclean and Maclean (1947), reiterating the same charge, state that " the term lipoid is now employed in such a vague and unsatisfactory sense that it is often by no means clear what it is intended to indicate." Overton (1901) used the term, not in its chemical sense, but to denote *all those cellular substances such as fat, fatty acids, cholesterol and lipids, whose only relationship is the physical property of a common solubility in certain inorganic solvents such as chloroform, ether, alcohol, etc.* In this discussion, it is proposed to use the term " lipoid " in Overton's sense, to denote fats, fatty acids, lipids such as galactolipids, and phospholipids such as lecithin, kephalin, sphingomyelin and cholesterol (which is a sterol), *for all these cell constituents are soluble in fat solvents and*

CHAPTER IX

THE SELECTIVE ACTION OF INHALATION ANÆSTHETICS ON THE CENTRAL NERVOUS SYSTEM

WHEN the body is exposed to an anæsthetic atmosphere containing an inhalation anæsthetic in an effective concentration, the first type of body tissue to be depressed in a characteristic fashion is the brain. It is possible to regulate the concentration of the anæsthetic in the anæsthetic atmosphere so that it depresses the functional activity of the brain but fails to depress all other types of tissue cells. This selective biological response of the body to inhalation anæsthetics is attributed to the fact that the brain is more susceptible to the depressing action of narcotics than any other type of body tissue and generally speaking it attains a state of anæsthetic equilibrium with the anæsthetic atmosphere more rapidly than any other type of body tissue.[1]

Haldane, in his work on the saturation and desaturation of the body with nitrogen, emphasised that it is a common mistake to assume that the rate of saturation of the body taken as a whole is a measure of the rate at which individual organs of the body saturate For example, when the body taken as a whole is half saturated to the pressure of nitrous oxide in the anæsthetic atmosphere, it is often assumed that the tension of nitrous oxide in solution in each and every type of body tissue has also risen to half the pressure of nitrous oxide in this atmosphere. This assumption is, of course, not true: it would obtain only if the body consisted of a homogeneous mass of cells with an equal blood supply to each and every type of body tissue. But Man's body is a heterogeneous cell system whose cells differ markedly both in consistency and function; moreover, the minute blood flow to individual organs and cells shows marked differences, not only as between different organs but also in the same organ at rest and at work

[1] This generalization may not be true of anæsthetics with a very high oil/water partition coefficient

prolonged. *Elément constant* consists of the lipoid content, in the Overton sense, of living cells; it does not vary in health or starvation and cannot be diminished without causing the death of the tissue. Bloor (1916, 1923, 1924) found that the lipoid, cholesterol and fatty acid content of normal blood was fairly constant, and Meyer and Schaffer (1913, 1914) found that the proportion of lipoid in most organs is comparatively constant. According to Leathes and Raper (1925) and Wright (1942) the brain, the kidneys, the spleen and the lungs contain only *élément constant*. The liver contains *élément variable* which, however, disappears during starvation and leaves an *élément constant* of constant proportion for the particular species. Maclean and Maclean (1927) state that the constant association of cholesterol, lipids and fats in every tissue cannot be regarded as accidental, and Mayer suggests that the constant proportion of cholesterol to total fatty acids determines the proportion of water taken up by cells and that water content increases as the cholesterol content.

In health, Man's body contains a constant proportion of water relative to his body weight, and the same can be said of animals. It is difficult to produce experimentally any material or lasting alteration in the plasma volume of blood or the water content of living cells, and in health the water content of tissue cells has a constant value for the species and for the particular organ of the species. Rubner (1923) and Robinson (1931) consider that tissue cells contain *bound water* in addition to *free water*, but only a very small proportion of the water content of the cell can be associated with colloid in the bound form. Hill (1930) challenges the conception of bound water and is of the opinion that nearly the whole of the water content of the cell is free, in the sense that it can dissolve substances added to it. In this discussion we are concerned only with free water.

In man and animals, there is reason to believe that each organ is characterised by a fixed proportion of lipoid to water. In Table 23 the weight of several organs of a 6-kilo dog and the percentage lipoid and water content of these organs, calculated from the work of Mayer and Schaffer (1913, 1914), are shown in column 1, 2 and 3. The coefficient of solubility of di-ethyl ether in water is 15·46 c.c. and its oil/water partition coefficient is 2·3 With these figures,

are insoluble in water. The force of the criticism above is not, in fairness, applied only to the biochemist. Current anæsthetic literature divides inhalation anæsthetics into two groups: the "oxygen-replacer" and the "lipoid-soluble" anæsthetics. An oxygen-replacer is said to "act in a purely physical manner by limiting the oxygen supply to the cerebral cortex" to act, that is, as a simple asphyxiant gas. It is said that a lipoid-soluble anæsthetic "probably enters cells containing lipoids through the cell membrane and temporarily poisons such cells, thus preventing them from using oxygen"—which suggests histotoxic anoxia. Di-ethyl ether is frequently cited as a lipoid-soluble anæsthetic: it has an oil/water partition coefficient of 2·3, while nitrous oxide with an oil/water partition coefficient of 3·4, is said to act as an oxygen-replacer. Ethylene is said to act "mainly as an oxygen-replacer but has slight lipoid-soluble action": this anæsthetic is 13 times more soluble in olive oil than in water. Such confused and incorrect terminology is inexcusable, for all the inhalation anæsthetics in common clinical use have an oil/water coefficient of more than unity and are soluble in lipoids. Since, moreover, fats and fat-like substances occur in every type of body cell and are indispensable to life, it follows that all the inhalation anæsthetics in common clinical use dissolve in cell lipoids. No direct proof of the specific function of lipoids is available and there is no evidence that the solution of a narcotic below its critical precipitation concentration, in the lipoids of living cells, poisons these cells or produces either narcosis or oxygen lack. And it is probable that the common property of lipoid solubility does nothing more than assist inhalation anæsthetics to concentrate at the site of their drug fixation in or on the cell surface

Mayer and Schaffer (1913, 1914) and Terroine and Weill (1913) divide body lipoids into two distinct groups; an *élément variable* and an *élément constant* *Elément variable* consists of the fat located in the storage depots throughout the body. It consists almost entirely of simple glycerol esters of fatty acids which are readily soluble in ether and slightly soluble in alcohol. *Elément variable* hardly concerns us in this discussion, for it absorbs gases and vapours very slowly because of its meagre blood supply and will approach full saturation only if anæsthesia is unwarrantably

TABLE 23.

A 6-KILO DOG.

Organ.	Weight	Lipoid content	Water content	Absorptive Capacity for Di-ethyl Ether		
				(Calculated)		(Observed)
		wet substance			at 25 mm. of Hg.	By Nicloux
	(Grams) 1	(%) 2	(%) 3	(C c.) 4	(Mgs) 5	(Mgs.) 6
Brain	58	9 6	74·6	869	94	76 9
Heart	50	2 5	77	639	69	70
Liver	324	3 5	68 7	3631	352	390
Kidneys	50	3 2	76	644	70	66
Spleen	26	2 8	77·7	339	37	31

(The weights of the organs of an average healthy 6-kilo dog quoted were kindly supplied by the Royal Veterinary College, London)

the absorptive capacity of these several organs for di-ethyl ether has been calculated, assuming that the solubility of di-ethyl ether in cell lipoids is the same as its solubility in olive oil, and the results are shown in column 4 of this Table. Nicloux (1907) observed the absorptive capacity in mgs. per 100 grams of substance of several organs of a dog for di-ethyl ether and from his figures the mass of di-ethyl ether absorbed by the organs of this 6-kilo dog have been calculated and are shown in column 6 of Table 23. In Nicloux's experiment, when death of the animal occurred, the di-ethyl ether content of arterial blood was 161 mgs., and that of mixed venous blood was 160 mgs. per 100 grams of blood; and it is clear that equilibrium in respect to di-ethyl ether had to all intents and purposes been assumed throughout the whole body of this dog. It has been calculated that 160 mgs. per 100 grams of blood represents a di-ethyl ether tension in solution of about 25 mm. of mercury, and since this is the calculated tension of di-ethyl ether in venous blood in Nicloux's experiment, it can be assumed that this was also the tension of di-ethyl ether in solutions in the individual organs of his dog when full saturation had been achieved In Table 23 the mass of di-ethyl ether in these several organs has been calculated in terms of the absorptive capacity of the organ in cubic centimetres for this anæsthetic at a tension of 25 mm. of mercury, and is shown in column 5. It is seen that the estimated absorptive capacity of these organs for di-ethyl ether in milligrams is of the same relative order as that observed by Nicloux and that the estimated mass of di-ethyl ether absorbed by particular organs corresponds fairly accurately with that observed by Nicloux.

The results obtained in Table 23, in the author's opinion, justify the use of the same method of calculation to estimate the absorptive capacity of the organs of a 70-kilo man for the inhalation anæsthetics in common clinical use Table 24 shows the weight and the lipoid and water content of several organs of a 70-kilo man, collated from the works of Koch and Mann (1907), Close (1934), Leathes and Raper (1925) and Bodansky (1934) The absorptive capacity of these several organs for nitrous oxide—oil/water partition coefficient 3·4 and coefficient of solubility in water 0 395 c c —has been calculated on the assumption that its solubility in cell lipoids is the same as its solubility in olive oil. It is

seen that the order of the absorptive capacity of these several organs for nitrous oxide in a man is the same as that of di-ethyl ether in the dog. When the lipoid-water content of these several organs in a dog and a man are compared and when it is remembered that the oil/water partition of nitrous oxide and di-ethyl

TABLE 25.

A 70-KILO MAN AT A RESTING METABOLIC RATE.

Organ	Minute blood flow per 100 grams of tissue	Blood flow per round of circulation for the whole organ.	Carrying Capacity for Nitrous Oxide of blood flow per round of circulation.
	(C.c.)	(C.c.)	(C.c.)
Brain	136	979	403 35
Heart	43	90	37·08
Liver	25 [1]	236	97·94
Kidneys	99	173	71·48
Spleen	58	30	12 57
Whole Body	—	4,500	1,854

[1] Arterial flow only

ether is as 3 4 to 2·3, this result might be expected if (as the author believes) solubility is the dominant factor in the uptake of inhalation anæsthetics by tissue cells.

Information regarding the minute blood flow through various organs of Man's body is scanty and meagre. In Table 25, figures quoted by Macleod (1930) of the minute blood flow at rest per 100 grams of tissue (as measured by the stromuhr method), and figures from other sources also, are given for the several organs cited in the last table. From these figures, the blood flow per round of circulation for each organ and the carrying capacity of this volume of blood for nitrous oxide has been calculated.

With the two relevant factors, viz. the absorptive capacity of the particular organ for nitrous oxide and the share of nitrous oxide bearing blood which it receives per round of circulation, the

TABLE 24.

A 70-KILO MAN.

Organ	Lipoid content (Wet)	Water content	Weight	Lipoid content	Water content	Absorptive Capacity for Nitrous Oxide.
	(%)	(%)	(Grams)	(Grams)	(Grams)	(C.c.)
Brain	12·8 [1,3]	76·42 [1]	1,440	184·3	1,100	682
Heart	2·2 [3]	80·3 [4]	420	9·24	337	145
Liver	2·5 [3]	76·9 [4]	1,892	47·3	1,455	828
Kidneys	2·9	82·5 [4]	350	10·2	288	127
Spleen	2·5	79·0 [4]	205	5·12	162	67
Spinal Cord	18·0 [2]	74·0 [4]	155	27·0	115	83
Whole Body	12·0 [4]	80·0 [3]	70,000	8,400·0	56,000	33,410

[1] Koch and Mann. [2] Bodansky. [3] Leathes and Raper. [4] Close.

seen that the order of the absorptive capacity of these several organs for nitrous oxide in a man is the same as that of di-ethyl ether in the dog. When the lipoid-water content of these several organs in a dog and a man are compared and when it is remembered that the oil/water partition of nitrous oxide and di-ethyl

TABLE 25.

A 70-KILO MAN AT A RESTING METABOLIC RATE.

Organ	Minute blood flow per 100 grams of tissue	Blood flow per round of circulation for the whole organ.	Carrying Capacity for Nitrous Oxide of blood flow per round of circulation.
	(C.c.)	(C.c.)	(C.c.)
Brain	136	979	403 35
Heart	43	90	37·08
Liver	25 [1]	236	97 94
Kidneys	99	173	71·48
Spleen	58	30	12 57
Whole Body	—	4,500	1,854

[1] Arterial flow only

ether is as 3·4 to 2·3, this result might be expected if (as the author believes) solubility is the dominant factor in the uptake of inhalation anæsthetics by tissue cells.

Information regarding the minute blood flow through various organs of Man's body is scanty and meagre. In Table 25, figures quoted by Macleod (1930) of the minute blood flow at rest per 100 grams of tissue (as measured by the stromuhr method), and figures from other sources also, are given for the several organs cited in the last table. From these figures, the blood flow per round of circulation for each organ and the carrying capacity of this volume of blood for nitrous oxide has been calculated.

With the two relevant factors, viz. the absorptive capacity of the particular organ for nitrous oxide and the share of nitrous oxide bearing blood which it receives per round of circulation, the

absorption coefficient of these several organs for nitrous oxide at rest has been estimated and the results are shown in Table 26. It is seen that the absorption coefficient of these several organs for nitrous oxide differs and that each organ absorbs nitrous oxide at a rate determined by its absorptive capacity for nitrous oxide and its blood supply.

Of all the organs cited in this Table, the brain has the largest absorption coefficient. It therefore absorbs this gas most rapidly and reaches a state of gaseous equilibrium with the pressure of nitrous oxide in the atmosphere breathed in a shorter time than do any of the other organs listed in Table 26. The remaining organs all of which are non-nervous tissues, attain a state of gaseous equilibrium with the anæsthetic atmosphere in an order determined by their individual absorption coefficient for nitrous oxide. Reference to Table 26 shows that the kidneys are the second type of tissue to reach full saturation and then, in order, the heart, the spleen, the liver, and finally the body taken as a whole.

The absorption coefficient of these several organs for the commonly used inhalation anæsthetics has been estimated in this fashion. The results are shown in Table 27, which shows that inhalation anæsthetics fall naturally into three groups. The first group consists of anæsthetics with a low oil/water partition coefficient such as acetylene, di-ethyl ether and nitrous oxide; the brain absorbs the members of this group most rapidly and then, in order, the kidneys, the heart, the spleen, and finally (of the organs listed) the liver. The next group is represented by ethylene whose oil/water partition coefficient is 13; in this group the kidneys absorb most rapidly and then, in order, the brain, the heart, the spleen, and finally the liver. The third group consists of anæsthetics with a very high oil/water partition coefficient such as cyclopropane, chloroform and it is presumed trichlorethylene and when the body is exposed to an atmosphere containing these anæsthetics, the order of their absorption by the organs cited in this Table is, the kidneys, *the heart*, the brain, the spleen, and finally the liver.

If the individual susceptibility of all types of body cells to the depressing action of inhalation anæsthetics was the same, the

TABLE 26.

A 70-KILO MAN AT A RESTING METABOLIC RATE.

Organ	Carrying Capacity of one round of blood for Nitrous oxide (C c.)	Absorptive Capacity for Nitrous Oxide (C c)	Absorption Coefficient for Nitrous Oxide	Absorption rate of Nitrous Oxide
Brain	403 35	682 0	10/16	Most rapid
Kidneys	71·48	127 21	10/18	↓
Heart	37 08	145 56	10/39	↓
Spleen	12 57	67 35	10/54	↓
Liver	97 94	828 24	10/84	Slowest
Whole Body	1.854 0	33,410·0	10/180	

$$\text{Absorption Coefficient} = \frac{\text{Carrying Capacity of its blood flow per round}}{\text{Absorptive Capacity of the whole organ}}$$

sequence of absorption of an effective concentration of an inhalation anæsthetic by the body cells would be the dominant factor in determining the biological response of the body to these anæsthetics. Thus, in the case of acetylene, di-ethyl ether, and nitrous oxide, the brain is the first organ to reach a state or anæsthetic equilibrium with the anæsthetic atmosphere and it would be depressed first, with the production of a state of anæsthesia. As absorption proceeded, the kidneys and then the heart, each in their turn, achieve a state of anæsthetic equilibrium with the atmosphere breathed. If the susceptibility of these organs to the action of narcotics was the same as that of the brain, each in its turn would be successively depressed, and, with cardiac depression, the subject would die During ethylene anæsthesia, the kidneys and then the brain would be successively depressed and shortly after anæsthesia had been established, the heart would achieve anæsthetic equilibrium with the anæsthetic atmosphere—a similarly fatal result. With anæsthetics such as cyclopropane, chloroform and trichlorethylene, however, the kidneys would be depressed and then when anæsthetic equilibrium was established between the heart and the anæsthetic atmosphere, the heart would be depressed and the subject would die before the brain could be acted on by these anæsthetics.

This depression of non-nervous tissues does not in fact occur in clinical practice, and death of the subject from cardiac failure is not the inevitable result of the absorption of the inhalation anæsthetics in common clinical use; for individual types of body cells vary very considerably in their susceptibility to the depressing action of narcotics. Of all the various types of body cells, those of the brain are most susceptible to the action of narcotics and are depressed by a lower concentration of a given narcotic than are other types of body cells And in a properly conducted anæsthetic, the concentration of the anæsthetic in the brain is an effective concentration, while in non-nervous cells the concentration of the anæsthetic is below the minimum threshold concentration necessary to depress them.

The kinetic formula, Concentration × Time = A Constant, implies that an infinite dilution of a drug can produce a biological response in living cells if infinite time is available, but the

TABLE 27.

A 70-KILO MAN AT A RESTING METABOLIC RATE.

Organ	Acetylene O/W p.c 1 89	Di-ethyl ether O/W p.c. 2 3	Nitrous Oxide O/W p c. 3·4	Ethylene O/W p.c. 13	Cyclopropane O/W p.c. 43	Chloroform O/W p.c. 64
Brain	10/14	10/16	10/16	10/22	10/41	10/39
Kidneys	10/17	10/18	10/18	10/15	10/18	10/16
Heart	10/39	10/39	10/39	10/26	10/36	10/30
Spleen	10/56	10/59	10/54	10/47	10/56	10/48
Liver	10/65	10/65	10/84	10/54	10/66	10/58
Whole Body	10/160	10/170	10/180	10/230	10/420	10/370

(O/W p.c. = Oil/Water partition coefficient.)

assumption does not hold, for there is a minimum threshold concentration below which a drug fails to produce its characteristic action on a given type of body cell; narcotics are no exception to this rule. Of all the types of body cells, those of the nervous system are most susceptible to narcotic action and are depressed in a characteristic fashion by a lower concentration of a narcotic than are non-nervous tissue cells. Graham (1929) has shown in animals that the concentration of di-ethyl ether required to paralyse striated muscle when applied locally is 3-4 times greater than that required to produce loss of muscle tone during inhalation anæsthesia with di-ethyl ether, that is when an effective concentration of this anæsthetic has been attained in the areas of motor co-ordination of the brain. Again, it is observed in clinical practice that the functional activity of non-nervous tissue cells is not depressed by concentrations of inhalation anæsthetic which are effective for the brain. Thus, the heart maintains an effective circulation and the liver continues to detoxicate reactive anæsthetics during anæsthesia, although the functional activity of these organs may be reduced in keeping with the diminution of the metabolic rate of the whole body which occurs by reason of the anæsthetic depression of the great adjustor mechanism, the brain. There is little doubt that the cells of the brain are depressed by a lower concentration of a given inhalation anæsthetic than any other type of body tissue; in clinical practice it is possible to regulate the partial pressure of an inhalation anæsthetic in the anæsthetic

most rapidly—is at the same time depressed by the lowest concentration of these anæsthetics. It follows that an effective concentration of these anæsthetics is achieved in the brain more rapidly than in any other type of body tissue and the resulting biological response permits the anæsthetist to regulate the partial pressure of these anæsthetics in the anæsthetic atmosphere, so that it is an effective concentration for the brain but is at the same time below the minimum threshold concentration necessary to depress all other types of body cells. In consequence, these anæsthetics exert a selective action on the brain to the exclusion of all non-nervous tissues.

Although ethylene, whose oil/water partition coefficient is 13, is absorbed more rapidly by the kidneys than by the brain, the concentration of ethylene necessary to depress the kidneys is greater than that required to depress the brain. If, therefore, the concentration of ethylene in the anæsthetic atmosphere is maintained below the minimum threshold concentration necessary to depress the kidneys but is at the same time an effective concentration for the brain, ethylene must then exert a selective action on the brain to the exclusion of all non-nervous tissue cells. This is readily achieved, for ethylene is a weak anæsthetic, and, in the conditions of clinical practice, the greatest possible partial pressure of ethylene which can be produced in the anæsthetic atmosphere is insufficient, in the absence of anoxia, to depress the areas of motor co-ordination of the brain and the vital medullary centres, much less the functional activity of the kidneys or any other type of non-nervous tissue cell.

Reference to Table 27 shows that the response of the body to cyclopropane, chloroform and trichlorethylene, whose oil/water partition coefficients are very high, is dominated by the fact that these three inhalation anæsthetics are absorbed more rapidly by the heart than by the brain. And if the partial pressure of these anæsthetics in the anæsthetic atmosphere is an effective concentration for the heart, their rapid uptake by this organ ensures that primary cardiac failure must occur, often before the anæsthetic depression of the brain is complete. In clinical anæsthetic practice, moreover, an effective concentration for the heart may unwittingly be readily produced, for all three anæsthetics are potent

anæsthetics with a very low solubility in whole blood By reason of these physical properties a state of anæsthetic equilibrium is rapidly obtained between alveolar air, and an anæsthetic atmosphere containing any one of these three anæsthetics and their solubility in whole blood is so small that minor alterations in their partial pressure in the anæsthetic atmosphere are immediately reflected in the anæsthetic content of blood leaving the pulmonary capillaries. On this account, and also because they are potent anæsthetics, a slight rise in their blood concentration produces an intense biological response. Pohl (1891) observed that in dogs a concentration of 0·035% of chloroform in arterial blood produced moderate anæsthesia, while fatal overdose was produced by 0·058% of chloroform in arterial blood. It is clear that the physical properties of these three inhalation anæsthetics, their potency and the sequence of their absorption by the body, combine to ensure that the use of overpressure to hasten their absorption will inevitably be followed by the rapid uptake of an effective concentration of these anæsthetics by the heart with cardiac arrythmias and/or primary cardiac failure. To use overpressure with cyclopropane, chloroform, or trichlorethylene is to court the disaster of primary cardiac failure. Unless means can be taken completely to eliminate their action on the heart and ensure that they exert a selective action on the brain, they must be considered unsuitable for use in clinical anæsthetic practice. The necessary conditions can be achieved if the concentration of these three anæsthetics in the anæsthetic atmosphere is an effective concentration for the brain, but is at the same time always below the minimum threshold concentration necessary to depress the heart and all other types of body cells. In this instance, when the brain has achieved anæsthetic equilibrium with the anæsthetic atmosphere it will be depressed in a characteristic fashion while all other types of body tissue, irrespective of the rate of their absorption, are unaffected; for when they are fully saturated the concentration of their contained anæsthetic is below the minimum threshold concentration necessary to depress them. This manœuvre forms the basis of what has been termed "the graduated method of induction," which is discussed in detail later. It effectively eliminates the influence of the sequence of

absorption of these three anæsthetics by the various types of body cells and ensures that the anæsthetic depression of the brain, to the exclusion of all other types of body cell, is determined solely by the fact that the brain is more susceptible to the action of narcotics and is depressed by a smaller narcotic concentration than other types of body cells.

It can be concluded that acetylene, di-ethyl ether, nitrous oxide, ethylene, and probably di-vinyl ether and ethyl chloride, exert a selective biological action on the cells of the brain in clinical anæsthetic practice. Cyclopropane, chloroform and trichlorethylene can be made to conform to this pattern of response, but if these anæsthetics are used with overpressure they produce a selective action on the cells of the heart with consequent cardiac arrythmias and/or primary cardiac failure.

References

1. Bodansky, M. (1934). "Introduction to Physiological Chemistry." p. 609. 3rd Ed John Wiley & Sons, New York.
2. Bloor, W. R. (1916). *J biol. Chem.* 25, 577
   (1923). *J. biol. Chem.* 56, 711
   (1924). *J. biol. Chem.* 59, 543.
3. Close, H. G. (1934). *Brit. med. J.* 1, 98.
4. Graham, H. T. (1929) *J. Pharmacol.* 37, 9.
5. Hill, A. V. (1930). *Proc roy Soc. B.* 107, 115
6. Koch, W., and Mann, S A. (1907-8). *P. Physiol.* 36, XXXVI.
7. Leathes, J. B (1910) "The Fats." 2nd Ed. p. 1, 98, 203. Longman Green & Co., London.
8. Mayer, A , and Schaeffer, G (1913) *J. Physiol Path. gén.* 15, 696, 889.
   (1914). *J. Physiol Path. gén.* 16, 1, 23
9. Macleod, J J R. (1930). "Physiology and Biochemistry in Modern Medicine" 8th Ed p. 427 Henry Kempton, London
10. Maclean, H., and Maclean, I S (1927). "Lecithin and Allied Substances." The Lipins. p 2, 181 Longman Green & Co., London
11. Nicloux, M. (1907). *C R Acad Clerm. Ferrand.* 144, 341.
12. Overton, E (1901) *Studien uber die Narkose.* Jena.
13. Pohl, J (1891) *Arch. exp. Path. Pharmak.* 28, 239
14. Robinson, W. (1931). *J. biol Chem.* 92, 699.
15. Rubner, M. (1923). *Abh. preuss. Acad Wiss* No. 1.
16. Terroine, E F , and Weill, J. 1913) *J. Physil. Path. gen* 15, 548.
17. Wright, S (1942) "Applied Physiology" 7th Ed. p. 674. Humphrey Milford, London.

increased, by stupor, first co-operative and then non-cooperative in character, and at length consciousness is lost and the functional activity of the higher centre of the brain is completely abolished. As the partial pressure of the anæsthetic in the anæsthetic atmosphere is gradually increased, it next becomes an effective concentration in respect to the area of sensory co-ordination of the brain and the ability to react in a reflex manner to external stimulus is lost. Next the concentration of the anæsthetic in the anæsthetic atmosphere achieves the threshold concentration necessary to depress the areas of motor co-ordination of the brain and muscle tone is lost in all striated muscle except the diaphragm. Finally, if the concentration of the anæsthetic in the anæsthetic atmosphere is further increased it becomes great enough to depress the functional activity of the vital medullary centres; the respiratory centre fails first and then, as the concentration of the anæsthetic rises and anoxia increases, the vasomotor centre and—as an end-result—the cardiac centre fail.

When anæsthetic administration ceases, these areas of functional activity recover in the reverse order, and it is clear that the sequence of recovery from inhalation anæsthesia is the same as from severe degrees of partial anoxia of short duration. Recovery from the effect of electrical convulsive therapy, as used in the treatment of the acute depressions, has been observed to follow an identical sequence of events. Thus the violent clonic spasm ended, breathing recommences after about 30-45 seconds, and then motor tone returns in the muscles of the trunk and extremities This is followed by the return of the ability to react in a reflex manner to external stimulus, then consciousness returns and with it the subject may enter a state of non-cooperative stupor which, in turn, merges into a state of co-operative stupor, finally, after an appreciable time, the memory returns and recovery is complete. Recovery from continuous electrical narcosis follows an identical sequence of events and, on occasions, recovery from concussion follows a similar course. The recovery from depressants as varied as anæsthetics, anoxia, electricity, and local cerebral trauma goes far to confirm the view that the susceptibility of the cells which constitute these various areas of functional activity of the brain is characteristic of the type of cell rather than of the

agent used to produce the depression and there is reason to believe that the cells of these different areas of functional activity of the brain vary in their individual susceptibility to depressants such as anæsthetics, anoxia, electricity, etc. The Higher Centres of the brain are most susceptible and are depressed by the lowest concentration of a given anæsthetic and then in order, the areas of Sensory Co-ordination of the brain, the areas of Motor Co-ordination of the brain, and, finally, the Vital Medullary Centres, in the order, the Respiratory Centre, the Vasomotor Centre, and the Cardiac Centre.

This fact can be used in practice to compel all the inhalation anæsthetics in common clinical use to conform to the standard pattern of biological response and the method of its application is as follows: The partial pressure of the inhalation anæsthetic in the anæsthetic atmosphere is adjusted so that it is an effective concentration for the higher centres of the brain but is at the same time below the threshold concentration necessary to depress all other types of body cell. When at length consciousness is lost—*and only then*—the partial pressure of the anæsthetic is increased so that it is an effective concentration for the areas of sensory co-ordination of the brain but is at the same time below the threshold concentration necessary to depress all other less susceptible types of body cells. When, in response to this atmosphere, the ability to react to external stimulus is lost—*and only then*—the partial pressure of the anæsthetic in the anæsthetic atmosphere is again cautiously increased until it is an effective concentration for the areas of motor co-ordination of the brain but is at the same time below the minimum threshold concentration necessary to depress the vital medullary centres and all other less susceptible types of nervous and non-nervous tissue cells. This is the greatest depth of anæsthesia desired or required in clinical practice; but should the partial pressure of the anæsthetic in the anæsthetic atmosphere inadvertently be increased still further, the vital medullary centres are depressed in the order, the respiratory centre, the vasomotor centre and—as an end-result—the cardiac centre; death then occurs from secondary cardiac failure. This method of administration, which has been termed for the purpose of this discussion the *graduated method of*

induction, takes no heed of differences which may exist in the rate of absorption of inhalation anæsthetics by the various areas of functional activity of the body. In point of fact, its object is to neutralise the effects of such differences and to ensure that the sequence of the biological response elicited is determined solely by the known differences in the susceptibility of specific areas of functional activity of the brain to inhalation anæsthetics. Clinical experience has shown that the graduated method of induction is the *only safe* method of administration for anæsthetics with a high oil/water partition coefficient and a low water solubility, such as cyclopropane, chloroform and trichlorethylene.

A graduated method of induction, however, results in a long-drawn-out anæsthetic induction which, as will be seen later, is to be deprecated. With certain anæsthetics, in the interest of the rapid absorption of the inhalation anæsthetic and in turn a rapid anæsthetic induction, a partial pressure of the anæsthetic in the anæsthetic atmosphere considerably greater than that required to depress the areas of motor co-ordination of the brain is frequently employed during anæsthetic induction in clinical practice. Thus, the effective concentration of di-ethyl ether in brain cells necessary to depress the areas of motor co-ordination of the brain and produce loss of muscle tone in striated muscle other than the diaphragm, is about 50 mm. of mercury. In clinical practice, however, a partial pressure of about 120 mm. of mercury, or 16 per cent. of di-ethyl ether in the anæsthetic atmosphere, is frequently employed in the interest of rapid absorption; this partial pressure of di-ethyl ether is more than twice the concentration necessary to depress the areas of motor co-ordination of the brain and is considerably greater than what is required to depress the vital medullary centres. In spite of this, when in clinical practice a partial pressure of 120 mm. of mercury of di-ethyl ether is built up in the anæsthetic atmosphere as rapidly as the pharyngeal and laryngeal reflexes permit, it is found that the sequence of the anæsthetic depression of the body follows the order of the susceptibility of the various areas of functional activity of the brain to narcotics, and is as follows: The higher centres of the brain are depressed first, next the areas of sensory co-ordination of the brain, and then the areas of motor co-ordination of the brain. When muscle tone in striated

muscles other than the diaphragm has been abolished, and when in consequence the tension of di-ethyl ether in the areas of motor co-ordination of the brain is about 50 mm. of mercury, the partial pressure of di-ethyl ether in the anæsthetic atmosphere is reduced to 50 mm. of mercury. This manœuvre, which is shown diagramatically in Figure 10, has the effect of equalising the tension of di-ethyl ether in the two gas systems, viz. the anæsthetic atmosphere on the one hand and, on the other, the areas of motor co-ordination of the brain, and they are now in a state of gaseous equilibrium. Moreover, as a result of this manœuvre the tension of di-ethyl ether in the higher centres and in the areas of sensory co-ordination of the brain must now rapidly fall to 50 mm. of mercury, and the tension of di-ethyl ether in the vital medullary centres and all other nervous and non-nervous tissues must remain below the minimum threshold concentration necessary to depress them, for it cannot rise above 50 mm. of mercury. If, however, the partial pressure of di-ethyl ether in the anæsthetic atmosphere is not reduced in this manner, the vital medullary centres are soon depressed and the order of their depression is, the respiratory centre, the vasomotor centre, and—as an end-result—the cardiac centre; death occurs from secondary cardiac failure. This form of induction, the very antithesis of a graduated induction, has been termed for the purpose of this discussion, induction by the use of *overpressure*. In the case of di-ethyl ether and other anæsthetics with a high water solubility and a relatively low oil/water partition coefficient, the use of overpressure results in a sequence of response of the body which is identical with that obtained when a graduated method of induction is employed; but the rate at which this response is produced is considerably hastened.

The sequence of biological response of the body which occurs when overpressure is employed with di-ethyl ether, and which occurs with all inhalation anæsthetics when a graduated method of induction is employed, is termed for the purpose of this discussion, "Standard Sequence of Response" of the body to blood-borne anæsthetics. It is defined as: The complete anæsthetic depression of the higher centres of the brain, followed in order by the complete anæsthetic depression of the areas of sensory

co-ordination of the brain, then the complete anæsthetic depression of the areas of motor co-ordination of the brain, and finally anæsthetic depression of the vital medullary centres in the order,

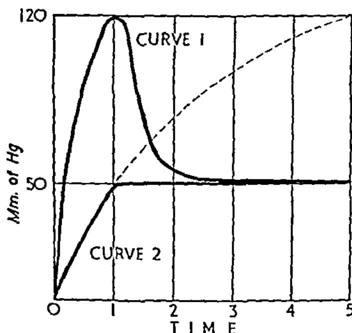


FIGURE 10.

A diagrammatic illustration of the use of overpressure with Di-ethyl ether.

Curve 1—Partial pressure of di-ethyl ether in alveolar air when exposed to a di-ethyl ether atmosphere at 120 mm of Hg. which was reduced to 50 mm of Hg at the end of the first period of time

Curve 2—Time-concentration curve of di-ethyl ether in arterial blood when exposed to this atmosphere. If the partial pressure of di-ethyl ether in this atmosphere is not reduced to 50 mm of Hg., at the end of the first period of time, its tension in arterial blood would follow the course of the stippled line

the respiratory centre, the vasomotor centre—and—as an end-result —the cardiac centre. This sequence of anæsthetic depression will be recognised as the only safe sequence of response, for overdose

results in *secondary cardiac failure*, and, in consequence, warning of impending overdose is clear and definite.

The production of a standard sequence of response when a graduated method of induction is employed is readily understood, but it is a more difficult problem to decide why the standard sequence of response occurs when overpressure is employed with di-ethyl ether. It is probable that the considerable disparity between the absorptive capacity and the carrying capacity of whole blood for di-ethyl ether is in part responsible, for this in a measure converts what appears to be gross overpressure into what is, in fact, a modified form of graduated induction. The simplest explanation of this phenomenon is, however, to assume that the sequence of absorption of di-ethyl ether by specified areas of functional activity of the brain coincides with the order of the susceptibility of these specific areas to narcotics. In this instance, an effective concentration of di-ethyl ether would be achieved most rapidly in the most susceptible areas, the higher centres, an effective concentration would be achieved next in the areas of sensory co-ordination which are next in order of susceptibility, and so on. It is pertinent, therefore, to examine the sequence of absorption of the various inhalation anæsthetics by the specific areas of functional activity of the brain.

The sequence of absorption of a given inhalation anæsthetic by particular organs of the body has been seen to depend upon the absorption coefficient of these several organs; this in turn is determined by the absorptive capacity of the particular organ and its blood supply. Since the nervous system is not a homogeneous mass of cells with an equal blood supply throughout, it is not unlikely that these two same factors, viz. absorptive capacity and blood supply, are also responsible for the rate at which a given inhalation anæsthetic is absorbed by specific areas of the nervous system.

Although the brain is an anatomical entity it consists of groups of cells, each of which plays a distinct and characteristic part in the physiological activity of the brain taken as a whole. Wright (1942) states: " The histological differences which exist between certain areas of the cortex are so great as to suggest that from this point of view at least we may regard the cerebral cortex not

as a single organ, but as a collection of organs." This is true, not only of the cerebral cortex, but also of the whole nervous system. Quastel & Wheatley (1933) assert: "There is every reason to believe that hypnotics are absorbed to different parts of the brain and that the specificity of their behaviour depends ultimately upon such specific absorption."

Bodansky (1934) states that "an outstanding difference in the composition of the grey and the white matter of the brain is the water content which in the former varies on an average between 83-85 per cent. and in the latter between 68-73 per cent." When his figures, which are shown in Table 29, are examined, it is seen that there is a second important difference, for the lipoid content of grey matter is 7·4 per cent. and that of white matter is 18 5 per cent. Bodansky states, moreover, that the spinal cord contains 74 per cent. of water and about 18 per cent. of lipoids, that peripheral nerves contain 60 per cent. of water, and that medullated nerves contain more cerebrosides than phospholipids, while the reverse is true of non-medullated nerves. McCollum (1930) observed in dogs that whole brain contained 74·6 of water and 9·6 per cent. of lipoids, grey matter 79 per cent. of water and 6 2 per cent. of lipoids, and white matter contained 74·2 per cent. of water and 11 9 per cent. of lipoids.

Table 29 shows that the grey matter of the nervous system contains a greater percentage of water and a smaller percentage of lipoids than white matter, and the lipoid-water content of individual types of nervous tissue can be expected to vary in keeping with the proportion of grey to white matter which they contain. Peripheral nerves which contain most white and least grey matter have a low water content of 60 per cent. and—it can be inferred—a high lipoid content, and medullated nerves contain more lipoid than non-medullated nerves. The spinal cord contains more grey matter and less white matter than peripheral nerves: its water content is greater than and its lipoid content less than that of peripheral nerves, but will vary at different levels. The greater proportion of grey matter in the medulla relative to the spinal cord implies a larger water content and a smaller lipoid content, and it can be expected that the cerebellum and then the cerebrum will progressively contain more water and less lipoid.

TABLE 29.

THE WATER AND LIPOID CONTENT OF SEVERAL TYPES OF NERVOUS TISSUE.

Tissue	Water Content %	Total Solids %		Total Lipoids %
Grey Matter—Man [1]	83 4	Protein	8 0	7·4
		Neurokeratin, an albumoid	0·4	
		Lecithin 3 0; Cephalin 0 7; Cerebrosides 3 0; Cholesterol 0·7	Total Lipoids	
		Inorganic matter	0 8	
White Matter—Man [1]	70 7	Protein	7 0	18 5
		Neurokeratin, an albumoid	3 0	
		Lecithin 5·0; Cephalin 3 5; Cerebrosides 5 0; Cholesterol 5 0	Total Lipoids	
		Inorganic matter	0 8	
Spinal Cord—Man [1]	74			18
Peripheral Nerves—Man [1]	60			
Medullated [1]		More cerebrosides than phospholipids		
Non-medullated [1]		More phospholipids than cerebrosides		
Whole Brain—Dog [2]	74 6			9·6
Grey Matter—Dog [2]	79			6·2
White Matter—Dog [2]	74·2			11·9

[1] Bodansky [2] McCollum

There is little doubt that the lipoid-water content of particular parts of the nervous system varies considerably; in general the water content decreases as the lipoid content increases. In consequence of this, it is to be expected that the individual absorptive

TABLE 30.

THE OBSERVED ABSORPTIVE CAPACITY OF SEVERAL AREAS OF FUNCTIONAL ACTIVITY OF THE CENTRAL NERVOUS SYSTEM OF THE RABBIT FOR DI-ETHYL ETHER AND CHLOROFORM.

Tissue	Absorptive Capacity (in milligrams per 100 grams of tissue) for			
	Di-ethyl ether	Chloroform		
	Oil/water partition coefficient 2·3	Oil/water partition coefficient 64.		
	(Hansen)	(Hansen)	(Nicloux & Yovanovitch)	
Cerebrum	115	30	52·5	52
Cerebellum	119	27	55·8	—
Medulla	133	39	75·5	57·4
Spinal Cord	161	—	—	59

capacity of the various parts of the nervous system for inhalation anæsthetics will vary as the lipoid-water content of the particular area and the oil/water partition coefficient of the particular anæsthetic.

Hansen (1925) exposed rabbits to a di-ethyl ether/air and a chloroform/air mixture, for a period of time sufficient to ensure that full saturation had been attained at the partial pressure of these anæsthetics. His observed results of the absorptive capacity of several parts of the central nervous system, together with similar observations made by Nicloux and Yovanovitch (1924), are shown in Table 30. It is seen that the cerebrum, which has the smallest lipoid content of these several areas of the central nervous system, has the smallest absorptive capacity for these predominantly fat-soluble anæsthetics. And as the lipoid content progressively

increases through the cerebellum, the medulla and the spinal cord, so also does the absorptive capacity of these parts of the central nervous system for di-ethyl ether and chloroform. Since the oil/water partition coefficient of di-ethyl ether is 2·3 and that of

TABLE 31.

THE OBSERVED ABSORPTIVE CAPACITY OF SEVERAL AREAS OF FUNCTIONAL ACTIVITY OF THE CENTRAL NERVOUS SYSTEM OF RABBIT FOR ETHYL ALCOHOL AND ACETONE (HANSEN 1925).

Tissue	Absorptive Capacity (in milligrams per 100 grams of tissue) for	
	Ethyl alcohol	Acetone
	Oil/water partition coefficient at 36° C 0 046	Oil/water partition coefficient at 36° C. 0·236
Cerebrum	123	209
Cerebellum	121	190
Medulla	112	181
Spinal Cord	109	—

chloroform 64, it is to be expected that the fat solubility of each anæsthetic should exercise a material influence upon the absorptive capacity of these several areas for each anæsthetic. And this is found to be the case, for it is seen that the medulla absorbs about 16 per cent. more di-ethyl ether than the cerebrum, while in Hansen's experiment, the medulla absorbs about 30 per cent., and and in Nicloux and Yovanovitch's first experiment, it absorbs about 37 per cent. more chloroform than does the cerebrum.

Hansen also observed the absorptive capacity of these several areas of the central nervous system for the predominantly water-soluble narcotics, ethyl alcohol and acetone, whose oil/water coefficients are less than unity. Table 31 shows that relative to di-ethyl ether and chloroform the order of the absorptive capacity of these several parts of the central nervous system is reversed; it is the cerebrum that has the largest absorptive capacity for ethyl

alcohol and acetone, and then, decreasingly, the cerebellum and the medulla, and last the spinal cord. Thus, predominantly water-soluble narcotics whose oil/water partition coefficient is less than unity are absorbed by these several parts of the central nervous system in keeping with the water content of each particular part, for the water content of the cerebrum is greatest, and it decreases progressively through the cerebellum the medulla to be the smallest in the spinal cord.

The order of the absorptive capacity of these several areas of the central nervous system for predominantly lipoid-soluble narcotics on the one hand, and on the other for predominantly water-soluble narcotics, goes far to establish the premise that a dominant factor in determining the absorptive capacity of a given tissue for a particular narcotic is the lipoid/water content of the tissue and the oil/water partition coefficient of the particular narcotic. On the one hand, the absorptive capacity of the medulla, for narcotics whose oil/water partition coefficient is less than unity, is less than that of the cerebrum. (As will be seen later, this limits the field of clinical usefulness of these narcotics; while they may be safely used in single hypnotic dosage they are unsuitable for use as anæsthetics in clinical practice.) On the other hand, the absorptive capacity of the medulla for narcotics whose oil/water partition coefficient is about 2 or greater, is materially larger than that of the cerebrum; and in the absence of other factors, these lipoid soluble narcotics are suitable for use as anæsthetics in clinical practice. The observations of Hansen and Nicloux and Yovanovitch show that the cerebrum has the smallest absorptive capacity for these lipoid-soluble anæsthetics; the capacities of the cerebellum and the medulla are progressively greater, and of the spinal cord, the greatest.

The minute blood-flow to various parts of the nervous system varies very considerably and the minute blood-flow per milligram of tissue is greater in the brain than in the spinal cord. Measurements show that the grey matter of the nervous system, in which the bodies of nerve cells lie, is more abundantly supplied with capillaries than is white matter; moreover, the capillary bed of both the grey and the white matter of the medulla is larger than that of the spinal cord. Woolf (1937) observed that the capillary

bed of the grey matter of the cerebral cortex was about twice that of peripheral nerves. This is approximately the order of oxygen consumption of these two types of nervous tissue, and there is little doubt that those parts of the nervous system which consume the most oxygen are most vascular. While it is clear that the viability of the cells of the nervous system is something quite different from the vascular requirements of these cells in normal conditions of life, total anoxia, produced by total circulatory arrest, kills the various types of cells of the nervous system at a speed which may be taken as a measure of their oxygen demands and in turn their vascularity. Reference to Table 28 shows the order of viability of several types of cells of the nervous system to anoxia produced by circulatory arrest; it suggests that the vascular need of the small pyramidal cells of the fourth layer of the cerebral cortex are greatest and that the need decreases through the Purkinji cells of the cerebellum, those of the medulla, the spinal cord, and is smallest for the peripheral nerves. Hence, of these several parts of the nervous system, the cerebrum has the smallest absorptive capacity, the largest minute blood supply and in turn the largest absorption coefficient for these lipoid soluble anæsthetics. The cerebrum absorbs lipoid soluble anæsthetics most rapidly and then, in order, the cerebellum, the medulla and the spinal cord. This conclusion is of value as indicating that the *medulla absorbs these predominantly lipoid-soluble anæsthetics more slowly than the rest of the brain*, but gives no information about the rate of absorption of lipoid-soluble anæsthetics by specific areas of functional activity of the cerebrum.

There is no datum regarding the absorptive capacity of specific areas of functional activity of the cerebrum for lipoid-soluble anæsthetics, but Gorodisskay (1925) investigated the cholesterol content, the phosphorus content of unsaturated phospholipids, and the total lipoid content as extracted with alcohol of several areas of functional activity of the cerebrum. Table 32, constructed from her results, shows the average amount of these constituents in the frontal pole, the post-central gyrus (areas 3, 1 and 2) and the pre-central gyrus (area 4) of twenty-five men and women. It is seen that, with the single exception of the phospholipid content of the left frontal pole, the cholesterol, the phospholipid and the

alcohol-soluble lipoid content is smallest for the frontal pole and increases progressively through the cortical areas of sensory co-ordination, to be greatest for the cortical areas of motor

TABLE 32.

THE OBSERVED CHOLESTEROL, PHOSPHORUS AND LIPOID CONTENT OF SEVERAL AREAS OF FUNCTIONAL ACTIVITY OF THE BRAIN OF MAN (GORODISSKAY 1925).

	Left side (Mgs. per cent of fresh substance)		
Tissue	Cholesterol	Phosphorus as unsaturated Phospholipids	Lipoids (Alcoholic) extract)
Frontal Pole	0·57	0.0690	2 37
Post-central gyrus (*sensory*)	0 80	0 0644	2 93
Pre-central gyrus (motor)	0 90	0 0811	3 04
	Right side (Mgs per cent. of fresh substance)		
Frontal Pole	0 59	0·0633	2 36
Post-central gyrus (sensory)	0·68	0 0693	2 87
Pre-central gyrus (motor)	0·79	0 811	3 22

co-ordination. It has been observed in general that the water content decreases as the lipoid content of nervous tissue increases. Since the frontal pole has the smallest lipoid content, it is probable that it has the largest water content; and that the water content decreases as the lipoid content increases, through the cortical areas of sensory co-ordination, to be smallest in the cortical areas of motor co-ordination If this is in fact the case—and the data presented seems to warrant this premise—it can be assumed that the absorptive capacity of the frontal pole for lipoid-soluble anæsthetics (such as di-ethyl ether, and chloroform) is smallest and that it progressively increases through the cortical areas of sensory co-ordination, the cortical areas of motor co-ordination.

the remaining areas of functional activity of the cerebrum and cerebellum in a yet undetermined sequence, to be largest for the medulla.

Scanty but concrete evidence is available of the blood supply of various areas of functional activity of the cerebrum. Woolf (1937) observed that the grey matter of the cerebral cortex has about 1080 millimetres of capillary length per milligram of tissue, while the corresponding index for white matter is about 300. This is approximately the order of the oxygen consumption of these two types of tissue. He found that the blood supply of the cerebral cortex differed from layer to layer. Within a single cortical zone vascularity was observed to increase from layer 1 to layer 4, and then to decrease through layer 5 and layer 6. The vascularity of layers 1 and 6 was of about the same order and layer 4, the internal granular layer, was 35-60 per cent. more vascular than layers 1 and 6. The greatest difference was observed in the parietal cortex where the vascularity of layer 4 was 60 per cent. greater than that of layers 1 and 6. Woolf states that those regions of grey matter which contain the greatest number of co-relating connections or synapses, or those with the largest total neural surface area, receive by far the most abundant blood supply and consume the greatest amount of oxygen. In general, the blood supply of sensory nuclei is greater than that of motor nuclei—a fact explained by the almost continuous activity of sensory neurones, as opposed to the more intermittent action of neurones concerned with motor acts. Woolf measured the average total length of blood vessels in millimetres per milligram of brain tissue His results are seen in Table 33 The parietal cortex, which contains the sensory and motor areas and is therefore metabolically an active region, has the greatest vascularity. The lower centres, the putamen and the globus pallidus, which represent an evolutionary older sensory and motor centre respectively, are metabolically less active They have a smaller blood supply than the cerebral cortex and the motor centre, the globus pallidus, has a smaller blood supply than that of the sensory centre, the putamen. Finally, Table 33 shows that the vascularity of peripheral nerves and white matter is less than half that of the parietal cortex.

There can be no doubt that there is a definite and consistent arrangement of capillaries in different parts of the nervous system and those parts which consume most oxygen are most vascular. The higher centres, the cerebral cortex, have the

TABLE 33.

THE VASCULARITY OF SEVERAL AREAS OF FUNCTIONAL ACTIVITY OF THE CENTRAL NERVOUS SYSTEM OF THE CAT (WOOLF 1937).

Average total length of blood vessels in millimetres per milligram of tissue.		
Cerebral cortex	971	100%
Cervical Sympathetic ganglion	737	85%
Putamen	640	73%
Globus Pallidus	509	58%
Peripheral nerves	412	47%
White matter	374	43%

largest blood supply and the cortical areas of sensory co-ordination are more vascular than the cortical areas of motor co-ordination. The lower centres have a smaller blood supply than the cerebral cortex and the motor nuclei are less vascular than the sensory nuclei. *Finally, the vascularity of the medulla is less than that* of the lower centres and its sensory nuclei have a larger blood supply than its motor nuclei. Hence there is reason to believe that the higher centres of the brain are most vascular, that its areas of sensory co-ordination are more vascular than its areas *of motor co-ordination and that the medulla is least* vascular.

If the absorptive capacity of each region of functional activity of the brain was the same, the blood supply to these several areas ensures that the higher centres would absorb narcotics most rapidly and then, in order, the areas of sensory co-ordination, the areas or motor co-ordination of the cerebrum and, finally, the medullary centres. The absorptive capacity of these several areas of functional activity is however, not the same, moreover, the order of their absorptive capacity for narcotics differs for predominantly lipoid-soluble anæsthetics and for predominantly water-soluble narcotics.

It has been concluded that the absorptive capacity of the frontal pole for lipoid-soluble anæsthetics is least and that it progressively increases through the cortical areas of sensory co-ordination, the cortical areas of motor co-ordination, the remaining areas of functional activity of the brain in a yet undetermined sequence, and finally is greatest for the medullary centres. If, as in the cerebral cortex, the sensory areas throughout had a smaller absorptive capacity than the motor areas—then such differences in the absorption coefficient of these several areas of functional activity, which exist by reason of known differences of vascularity, would be correspondingly accentuated. It can be concluded that the vascularity of specific areas of functional activity of the brain combines with the absorptive capacity of these areas for lipoid soluble anæsthetics to ensure that the higher centres of the brain, which contain the most susceptible cells, have the largest absorption coefficient and absorb lipoid-soluble anæsthetics most rapidly. Then follow, in order of susceptibility and absorption coefficient, the areas of sensory co-ordination, the areas or motor co-ordination and, finally, the vital medullary centres. It is clear that, with lipoid-soluble anæsthetics, an effective concentration is achieved first in the higher centres of the brain, next in the areas of sensory co-ordination, then in the areas of motor co-ordination, and finally—when overdose occurs—in the vital medullary centres and when lipoid-soluble anæsthetics are correctly administered, the biological response elicited follows this sequence

There is little doubt that the response of the brain to a given narcotic depends upon the sequence in which an effective concentration of the narcotic is achieved in each of the several areas of functional activity of the brain. This is determined by the individual susceptibility of these several areas of functional activity to narcotics, and by the individual absorption coefficient of these several areas for the particular narcotic, which in turn depends upon the blood supply of the area and its absorptive capacity for the given narcotic. Of these three factors, *the susceptibility and blood supply of each area of functional activity are constants, while the absorptive capacity of a given area for a particular narcotic varies as the oil/water partition of the narcotic.* And

there is little doubt that the order of the absorptive capacity of the several areas of functional activity of the brain for lipoid-soluble anæsthetics is a dominant factor in determining the sequence of anæsthetic depression produced by these anæsthetics

Reference to Table 31 shows that the order of the absorptive capacity of these several areas of the brain for predominantly water-soluble narcotics (such as ethyl alcohol and acetone) is the reverse of that which applies in the case of lipoid-soluble anæsthetics. When the blood supply of these several areas of functional activity is taken into account, the order of their absorptive capacity for water-soluble narcotics is unlikely to reverse the sequence of absorption of these narcotics by these areas of the nervous system relative to lipoid-soluble anæsthetics; this is confirmed by clinical experience. It can, however, be expected materially to modify the character of absorption by these areas. Thus, an effective concentration of these predominantly water-soluble narcotics will be achieved in the cerebrum more slowly, and in the cerebellum and the medulla more rapidly, than is the case with lipoid-soluble anæsthetics. Hence, the broad spacing between the successive depression of these specific areas of functional activity, which is so characteristic of lipoid-soluble anæsthetics, will be narrowed. when an effective concentration of these water-soluble narcotics is employed, it is to be expected that the medulla will be depressed, coincidentally with (or soon after) the higher centres of the brain. And this is precisely the response elicited when an effective concentration of ethyl alcohol is used in Man Thus, when the blood alcohol is less than 2 mgs. per c.c., the ability to control emotions, is impaired and the speed and accuracy of all reflexes is reduced below normal. When the blood alcohol is increased to 2-3 mgs per c.c., self-control is greatly impaired, speech becomes slovenly, the gait is unsteady and the accuracy with which skilled movements are performed is considerably reduced. When the blood alcohol rises above 3 mgs. per c.c , deep sleep passing to coma with depression of the vital medullary centres may produce death from respiratory failure: *there is very little interval between loss of consciousness and dangerous depression of the vital medullary centres.* In like manner, acetone produces early stimulation and then depression of the

respiratory centre soon after consciousness has been lost. In each instance, the biological response produced is a distortion of the standard sequence of response, and the early depression of the vital medullary centres renders these predominantly water-soluble narcotics unsuitable for use as anæsthetics in clinical practice.

If only the central nervous system is considered, it must be inferred that all lipoid-soluble anæsthetics are suitable for use in clinical anæsthetic practice, for they depress the central nervous system in the standard sequence. When, however, the sequence of absorption of lipoid-soluble anæsthetics by the body taken as a whole is considered, this conclusion must be modified.

Reference to Table 27 shows that the sequence of absorption of lipoid-soluble anæsthetics with an oil/water partition co-efficient of more than 1·89 and less than about 4 is brain, kidneys, heart, etc. It follows, when overpressure is used with di-ethyl ether (which has an oil/water partition co-efficient of 2·3), that its rate of absorption is hastened; and in spite of the fact that the partial pressure of di-ethyl ether may be considerably greater than that required to depress the vital medullary centres, the sequence of absorption of di-ethyl ether is such that the higher centres of the brain are first depressed, next the areas of sensory co-ordination, and then the areas of motor co-ordination lose their functional activity. In a correctly managed induction, the partial pressure of di-ethyl ether in the anæsthetic atmosphere is now reduced to about 50 mm. of mercury; but if this is not done, an effective concentration of di-ethyl ether is next achieved in the vital medullary centres and death occurs from secondary cardiac failure produced by the successive depression of the respiratory centre, the vasomotor centre and, as an end result, the cardiac centre. *And it is significant that even when over-pressure is used with di-ethyl ether, the sequence of absorption of this anæsthetic makes it impossible for an effective concentration to be achieved in the heart: primary cardiac failure is impossible with this anæsthetic.* The disparity between the absorptive capacity and the carrying capacity of whole blood for di-ethyl ether considerably reduces the effect of overpressure and, in consequence, materially reduces the possibility of inadvertant overdose. *Hence, irrespective of the method of the administration of di-ethyl ether, the response of the*

body to its action is always the standard response and death invariably results from secondary cardiac failure.

It can be expected that the biological response of the body to di-ethyl ether indicates the pattern of behaviour of inhalation anæsthetics with similar physical properties. The sequence of absorption of acetylene and nitrous oxide by various types of body tissue, as shown in Table 27, is of the same order as that of di-ethyl ether. And if absorptive capacity depends upon the lipoid-water content of the tissue and the oil/water partition coefficient of the anæsthetic, then it can be assumed that the sequence of absorption of acetylene and nitrous oxide is the same as that of di-ethyl ether, for their oil/water partition coefficients are respectively 1·89 and 3 4. Di-vinyl ether and ethyl chloride always produce the standard response when a graduated method of induction is employed Until accurate observations of the oil/water partition coefficients of these two anæsthetics are available, it is impossible to estimate accurately the sequence of their absorption and, therefore, the response of the body to their action when overpressure is used. But clinical experience indicates that the standard sequence of response *is always produced* when overpressure is used with these two anæsthetics, and this suggests that their physical properties are similar to that of di-ethyl ether. But, they are volatile and potent anæsthetics. Because the disparity between the absorptive capacity and the carrying capacity of whole blood for ethyl chloride and probably for di-vinyl ether is considerably less than is the case with di-ethyl ether, *overdose with secondary cardiac failure may readily be produced in clinical practice, if overpressure is imprudently used*

Hence, lipoid-soluble anæsthetics whose oil/water partition coefficient lies between 1 89 and 4 are absorbed by the brain more rapidly than by any other type of tissue, and their sequence of absorption by the brain itself is the standard sequence. It follows that the response of the body to their action is always the standard response: *with these anæsthetics death always occurs from secondary cardiac failure*

When a graduated method of administration is employed with anæsthetics whose oil/water partition coefficient is 43 and greater, the standard sequence of biological response may be produced in

clinical anæsthetic practice. This is in marked contrast to the distorted sequence of response which occurs when overpressure is used with these highly lipoid-soluble anæsthetics, for primary cardiac failure, either a vagal inhibition of the heart or ventricular fibrillation, may occur even before the higher centres of the brain have been completely depressed. Primary cardiac failure during anæsthetic induction is characteristic of a chloroform induction with overpressure and this distortion of the standard sequence of response may be attributed either to a central effect on the cardiac centre in the medulla, or to a local effect upon the heart itself.

Evidence has been discussed which indicates that the sequence of absorption of chloroform by the specific areas of functional activity of the brain is the same as that of di-ethyl ether. An effective concentration of chloroform is therefore achieved in the medulla late in absorption, and this suggests that the primary cardiac failure, which occurs *early in induction* when overpressure is used with chloroform, is not a central effect. Reference to Table 27 shows that the absorption coefficient of the heart for chloroform is greater than that of the brain taken as a whole. In consequence of this, the heart reaches a state of equilibrium with a chloroform atmosphere more rapidly than the brain taken as a whole and, it must be inferred, more rapidly than the cardiac centre, for the medulla has the smallest absorption coefficient for chloroform of the various areas of functional activity of the brain, and the cells of the cardiac centre are amongst the last cells of the brain to achieve anæsthetic equilibrium with a chloroform atmosphere That the heart assumes a state of anæsthetic equilibrium with the chloroform atmosphere more rapidly than does the vital medullary centres, is a fact of no consequence during a graduated induction when the partial pressure of chloroform in this atmosphere is always below the minimum threshold concentration necessary to depress the heart. If, however, overpressure is used and the partial pressure of chloroform in the anæsthetic atmosphere is an effective concentration for the heart, there is reason to believe that an effective concentration of chloroform will be achieved in the heart itself before the uptake of chloroform by the medulla has produced an effective concentration of this anæsthetic in the cardiac centre. It seems probable that primary cardiac

failure during chloroform anæsthesia, when overpressure is used, is due to a local effect upon the heart itself.

The occurrence of primary cardiac failure during chloroform anæsthesia before the higher centres of the brain have been completely depressed, suggests however, that the rapid absorption of chloroform by the heart is not the only factor concerned; there is evidence that a heart depressed by chloroform is particularly susceptible to the effects of sympathetic overaction or excess of adrenaline. Thus, Wright (1942) states: "the liability to extrasystoles, spontaneously or on afferent stimulation which is so characteristic of a lightly chloroformed animal, is abolished by the removal of the hypothalamus." The hypothalamus and more particularly the posterior hypothalamic nuclei mediate sympathetic action and stimulation of these nuclei produces secretion of adrenaline, a rise of blood pressure and increased cardiac action such as acceleration of the heart beat, shortening of the A.V. conduction time and extrasystoles. Goodman Levy (1912) showed during chloroform anæsthesia that an injection of adrenaline or any factor such as excitement, struggling and strong external stimulus produced, more often than not, syncope due to ventricular fibrillation. An injection of adrenaline or stimulation of this character does not produce this result during di-ethyl ether anæsthesia. There is little doubt that *the coincident presence in the heart of a certain critical concentration of chloroform and excess of adrenaline* is responsible for the ventricular fibrillation which may occur during a chloroform induction. Primary cardiac failure most often occurs during the non-cooperative stupor stage of chloroform induction, and it is during this stage of anæsthesia that the secretion of adrenaline is likely to be greatest; but at this early stage of chloroform induction it is unlikely—even when overpressure is used—that the concentration of chloroform absorbed by the heart is, *per se*, sufficient to interfere materially with the functional activity of the heart. This suggests that early in chloroform anæsthesia, a concentration of chloroform may be absorbed by the heart which is insufficient to interfere with the functional activity of the heart, but is sufficient to render it vulnerable to degrees of adrenaline excess or external stimulus which normally would not produce a harmful effect In a normal heart this critical concentra-

tion of chloroform can be produced early in anæsthesia only if overpressure is used. Macleod (1930) states that the bundle of His and its two branches have a liberal blood supply. This suggests that the absorption of chloroform by this tissue, for which it has a low haft-druck, is more rapid than by the myocardium, and overpressure during chloroform anæsthesia may well produce the early depression of the rate of conduction of the A.V. bundle. Since depression, and not increased excitability and conductivity of the conducting mechanism, is responsible for extrasystoles, cardiac arrythmias and ventricular fibrillation, it can be assumed that these arrythmias may be attributed to the early absorption of chloroform by the A.V. bundle with consequent depression of the functional activity of this tissue. But adrenaline also shortens the conduction time and diminishes the refractory period of the myocardium, and if the uptake of chloroform is sufficient to slow the rate of conduction, a set of circumstances favourable for the onset of circus movement is produced, viz., a slow rate of conduction, a short refractory period and perhaps a large ring. This set of circumstances may result in ventricular extrasystoles arising in one or many foci and this is followed by rapid almost regular undulations of the ventricle from which recovery is possible. Finally, if these conditions continue to act, incoordinate contractions of the myocardium commence and with this fibrillation: the heart dilates, the blood pressure falls to zero, and death occurs

In the past, primary cardiac failure early in chloroform anæsthesia has also been attributed to a vagal inhibition of the heart. In man, vagal stimulation depresses impulse formation, conductivity, contractibility, and, in fact, all the activities of the heart As a result, cardiac output is greatly reduced in volume and the systolic blood pressure may fall to zero within a few seconds of the commencement of vagal overaction and this in turn results in cerebral anæmia with loss of consciousness. This is the mechanism which produces a simple fainting attack, and when a vagal inhibition of the heart is produced in normal conditions of life, either the ventricles assume an independent rate or the vagal escape mechanism is successful in spontaneously re-commencing the heart

failure during chloroform anæsthesia, when overpressure is used, is due to a local effect upon the heart itself.

The occurrence of primary cardiac failure during chloroform anæsthesia before the higher centres of the brain have been completely depressed, suggests however, that the rapid absorption of chloroform by the heart is not the only factor concerned; there is evidence that a heart depressed by chloroform is particularly susceptible to the effects of sympathetic overaction or excess of adrenaline. Thus, Wright (1942) states: "the liability to extrasystoles, spontaneously or on afferent stimulation which is so characteristic of a lightly chloroformed animal, is abolished by the removal of the hypothalamus." The hypothalamus and more particularly the posterior hypothalamic nuclei mediate sympathetic action and stimulation of these nuclei produces secretion of adrenaline, a rise of blood pressure and increased cardiac action such as acceleration of the heart beat, shortening of the A.V. conduction time and extrasystoles. Goodman Levy (1912) showed during chloroform anæsthesia that an injection of adrenaline or any factor such as excitement, struggling and strong external stimulus produced, more often than not, syncope due to ventricular fibrillation. An injection of adrenaline or stimulation of this character does not produce this result during di-ethyl ether anæsthesia. There is little doubt that *the coincident presence in the heart of a certain critical concentration of chloroform and excess of adrenaline* is responsible for the ventricular fibrillation which may occur during a chloroform induction. Primary cardiac failure most often occurs during the non-cooperative stupor stage of chloroform induction, and it is during this stage of anæsthesia that the secretion of adrenaline is likely to be greatest, but at this early stage of chloroform induction it is unlikely—even when overpressure is used—that the concentration of chloroform absorbed by the heart is, *per se*, sufficient to interfere materially with the functional activity of the heart. This suggests that early in chloroform anæsthesia, a concentration of chloroform may be absorbed by the heart which is insufficient to interfere with the functional activity of the heart, but is sufficient to render it vulnerable to degrees of adrenaline excess or external stimulus which normally would not produce a harmful effect. In a normal heart this critical concentra-

uptake of chloroform by the heart, which occurs when overpressure is used, can be looked upon as the indispensable factor responsible for the production of primary cardiac failure, while excess of adrenaline or vagal overaction are occasional factors whose presence may precipitate the calamity, which occurs without warning.

Wittingly to use overpressure during a chloroform induction implies, therefore, either ignorance or stupidity. It has been seen, however, that a slight rise in the partial pressure of chloroform in the anæsthetic atmosphere is immediately reflected in its blood concentration, and since chloroform is a potent narcotic, a slight rise in its blood concentration results in a material increase in the intensity of its narcotic action. Hence, even when this anæsthetic is administered with skilful care, *overpressure may be unwittingly employed*, for it is difficult to control the partial pressure of a relatively involatile anæsthetic vapour in inspired air. Because of this same property, inadvertent overdose, with secondary cardiac failure, may occur during chloroform induction. Finally, when the level of chloroform anæsthesia is greater than complete sensory loss, and less than is necessary to depress the vital medullary centre, cardiac arrythmias may occur spontaneously in the aged and also in subjects whose cardiac reserve is impaired. At this level of anæsthetic depression the excessive secretion of adrenaline is impossible and vagal overaction is improbable; these cardiac arrythmias, which must be looked upon as the precursors of ventricular fibrillation, can be attributed to the uptake of an effective concentration of chloroform by the A-V bundle which is depressed in these subjects by a smaller concentration of chloroform than in a normal subject. Finally, adrenaline must never be injected during chloroform anæsthesia

It can be concluded that chloroform is a potent relatively non-volatile anæsthetic vapour whose partial pressure in inspired air is difficult to control. But the standard safe sequence of anæsthetic response can be produced in a healthy subject with chloroform if a graduated method of induction is employed and if emotional and/or physical stress is avoided throughout anæsthetic induction. In a healthy subject, when overpressure is employed with chloroform and/or when emotional and physical stress is permitted to act

at a normal rhythm The mechanism of vagal escape is as follows·—When syncope occurs as the result of a vagal inhibition of the heart, blood accumulates in the great veins and the right auricle, and venous pressure rises with consequent distention of the right heart. The local stimulation produced by this stretching of the myocardium and the central stimulation of the cardiac centre through the afferent nerve endings in the right heart from the same cause, combine with the asphyxial effect on the vasomotor centre to re-commence the normal rhythmic action of the heart In a heart whose conductivity and, perhaps, contractibility are already depressed by the rapid absorption of chloroform produced by overpressure, vagal overaction may cause syncope from which the heart does not spontaneously escape, for it fails to respond to the degree of stretching produced by the venous distention of the right heart. The vagal escape mechanism, therefore, fails. Syncope is complete and will remain so unless prompt and skilful treatment is instituted immediately. Since the introduction of atropine as a pre-anæsthetic medicant, vagal inhibition of the heart is relatively infrequent during chloroform anæsthesia, for atropine in appropriate dosage inhibits the action of acetylcholine released in the heart and other para-sympathetic effectors. Even after pre-medication with atropine and/or with scopolamine, which has a similar action, it must be realized that appropriate local stimulation during light anæsthesia may result in vagal overaction, for cardiac arrythmias occur about twice as frequently during operations on the neck as during surgical interferences on other sites.

Of the two types of primary cardiac failure which may occur during a chloroform induction, ventricular fibrillation is the most serious, for relief is impossible, unless and until the incoordinate contractions of the ventricular musculature are arrested. If this can be accomplished successfully by the intra-myocardial injection of 3-10 c c of a 1 per cent solution of procaine, as recommended by Lampson, Shaeffer and Lincoln (1948), it may then be possible to re-commence effective contractions of the heart with cardiac massage After a vagal inhibition of the heart, the prompt institution of cardiac massage will frequently be successful in re-commencing effective cardiac contractions. In each instance, *the rapid*

spontaneously during deep cyclopropane anæsthesia when over-pressure is used. The absence of cardiac arrythmias and/or primary cardiac failure during cyclopropane induction might well be attributed to the speed at which anæsthetic induction can be achieved with this potent non-irritating anæsthetic gas. Consequently the non-cooperative stupor stage of cyclopropane anæsthesia is very short; it has been observed that less than 3 per cent. of subjects exhibit excitement during cyclopropane induction. Since this is the period during any anæsthetic when the secretion of adrenaline is greatest, it can be concluded that swift induction is a factor which reduces the secretion of adrenaline during this period of cyclopropane anæsthesia to the smallest proportions. But Waters (1936) observed that in dogs the intravenous injection of adrenaline does not cause ventricular fibrillation during light cyclopropane anæsthesia; and in subjects anæsthetised to the level of complete sensory loss—Guedel's second plane of surgical anæsthesia—the injection of 1-200,000 adrenaline in the interest of hæmostasis has never been observed to affect the rhythm of the heart. This implies that the uptake of cyclopropane by the heart (relative to its uptake by the brain) is slower than that of chloroform, and that, in anæsthesia to the level of complete sensory loss, the concentration of cyclopropane absorbed by the heart is insufficient to render this organ susceptible to the action of adrenaline.

Reference to Table 27 shows that the estimated absorption coefficient of the heart for cyclopropane, viz. 10/36, is greater, but not very much greater than that of the brain taken as a whole, viz. 10/41, and this is in contrast to the significant difference in these two values for chloroform. There is an indication, therefore, that those areas of functional activity of the brain which absorb lipoid-soluble anæsthetics most rapidly—the higher centres and the areas of sensory co-ordination—reach anæsthetic equilibrium with a cyclopropane atmosphere more rapidly than the heart and those areas of the brain—such as the areas of motor co-ordination, and the medulla—which absorb lipoid-soluble anæsthetics most slowly, reach anæsthetic equilibrium with a cyclopropane atmosphere at a slower rate than the heart. And it can be concluded that the sequence of absorption of cyclopropane is such that, during anæsthesia to the level of complete sensory loss, the concentration of

during chloroform induction, or when adrenaline is injected, this anæsthetic may produce a distorted sequence of response with primary cardiac failure. This disaster is even more likely to occur in subjects whose cardiovascular system is abnormal. In these subjects cardiac arrythmias, which are to be looked upon as the precursors of ventricular fibrillation, may occur during anæsthetic maintenance with chloroform. The distorted sequence of response which may occur with this anæsthetic is attributed primarily to the sequence of its absorption by the body and secondarily to the fact that unwitting overpressure with chloroform can happen so readily. Quite apart from the protoplasmic degeneration of the kidneys, the heart and the liver which may follow a chloroform administration, chloroform must be considered a dangerous anæsthetic because of the distorted sequence of response which may so readily occur in clinical anæsthetic practice. In the opinion of many observers, chloroform should not be used in clinical anæsthetic practice.

Cyclopropane is a potent, non-irritating, lipoid-soluble anæsthetic gas; its oil/water partition coefficient is 43. Because it is lipoid-soluble, cyclopropane is absorbed by the several areas of *functional activity of the brain in the same sequence as di-ethyl* ether and chloroform, and, since its lipoid solubility is very high, it is absorbed (as shown in Table 27) more rapidly by the kidneys and the heart than by the brain taken as a whole. Hence its sequence of absorption is of the same order as that of chloroform. When a graduated method of induction is used with cyclopropane the standard safe sequence of biological response is produced. And a graduated method of induction can be carried out more accurately with cyclopropane than with chloroform, for cyclopropane is an anæsthetic gas above its critical temperature, and its partial pressure in the anæsthetic atmosphere can be more accurately controlled than that of chloroform.

When overpressure is used with cyclopropane, a local effect upon the heart can be expected, and the pattern of the biological response of the body to its action can be expected to be similar to that of chloroform. But it differs from chloroform, *for neither ventricular fibrillation nor vagal inhibition of the heart occurs during cyclopropane induction*, but as with chloroform, cardiac arrythmias and even primary cardiac failure may occur

adrenaline which they used, had a greater sensitizing effect on the "ventricular autonomic tissue" than either chloroform or ether. When measured by the response of the heart to the intravenous injection of adrenaline, there is little doubt that, as cyclopropane anæsthesia deepens beyond the level of complete sensory loss, the functional activity of the heart, probably that of the A-V bundle, may be materially depressed. Because, at this level of anæsthetic depression, adrenaline can be eliminated as a factor, the cardiac irregularities which occur during deep cyclopropane anæsthesia may be attributed solely to the uptake of cyclopropane by the heart itself, and particularly by the junctional tissue of the heart.

The response of the heart to adrenaline injected intravenously strengthens the conclusion already drawn that the rate of absorption of cyclopropane by the heart is slower than that of the higher centres and the areas of sensory co-ordination of the brain, but is more rapid than that of the areas of motor co-ordination and the medulla. It follows, therefore, when cyclopropane anæsthesia is deepened beyond the level of complete sensory loss, that the heart reaches anæsthetic equilibrium with the cyclopropane atmosphere more rapidly than the areas of motor co-ordination and the medulla. This circumstance does not produce cardiac irregularities in a healthy subject if the partial pressure of cyclopropane in the anæsthetic atmosphere is always below the threshold concentration necessary to depress the heart tissue; loss of muscle tone and, in turn, depression of the vital medullary centres proceed in the standard sequence, and death occurs from secondary cardiac failure. If, however, overpressure is inadvertently used at this stage of cyclopropane anæsthesia, and the partial pressure of cyclopropane in the anæsthetic atmosphere is sufficient to depress the functional activity of the heart, the rapid uptake of cyclopropane by the heart may produce a concentration of this anæsthetic in the heart itself, which is sufficient to depress its functional activity; cardiac arrythmias will occur before the concentration of cyclopropane in the areas of motor co-ordination and the medulla is sufficient completely to depress motor tone or the vital medullary centres Such cardiac irregularities are rapidly abolished if the partial pressure of cyclopropane in the anæsthetic atmosphere is immediately reduced to zero, for this effects an equally rapid excretion of cyclo-

cyclopropane which can be attained in the heart is neither sufficient to modify the functional activity of the heart nor to render it susceptible to the action of adrenaline. Moreover, the secretion of adrenaline is reduced to minimal proportions by the swift induction which is possible with cyclopropane; the absence of cardiac arrythmias and/or primary cardiac failure during cyclopropane anæsthesia to the level of complete sensory loss may be attributed to the character of its absorption by the body and to the absence of excess of adrenaline during this period of cyclopropane anæsthesia.

In clinical anæsthetic practice, it has been observed that irregularities of the heart occur spontaneously in healthy subjects as cyclopropane anæsthesia deepens beyond the level of complete sensory loss. The first sign of cardiac involvement consists of bradycardia or, less frequently, tachycardia. This is followed by cardiac arrythmia, which Thienes (1941) identified as ventricular extrasystoles. Unless the concentration of cyclopropane in the anæsthetic atmosphere is immediately reduced, this arrythmia may be followed by ventricular fibrillation

When the areas of sensory co-ordination of the brain have been completely depressed, emotional and physical stress is not possible and the body reacts only to intense proprioceptive stimuli. And there is reason to believe that, as anæsthesia deepens beyond this level of depression, excessive secretion of adrenaline is no longer possible. It is most unlikely, therefore, that adrenaline is a factor in the production of the cardiac arrythmias occuring when cyclopropane deepens beyond the level of complete sensory loss. But Waters (1936) observed in dogs that an intravenous injection of adrenaline, which did not produce ventricular fibrillation during light cyclopropane anæsthesia, produced this form of primary cardiac failure during deep cyclopropane anæsthesia. Hence, just as the heart is rendered susceptible to adrenaline during light chloroform anæsthesia, so also in deep cyclopropane anæsthesia the heart is rendered vulnerable to adrenaline injected intravenously in amounts which in normal conditions of life, or in light cyclopropane anæsthesia, do not produce a harmful effect. And the observations of Meeks, Hathaway and Orth (1937) led them to conclude that cyclopropane, as judged by the standard injection of

to abolish this abnormal cardiac reaction, it soon becomes apparent in the unsuitable subject that the partial pressure of cyclopropane which permits regular cardiac action is insufficient to maintain anæsthesia to the level of complete sensory loss. In such subjects the choice clearly lies between adequate anæsthesia, with, on the one hand, cardiac irregularities and the risk of primary cardiac failure and, on the other hand, the absence of cardiac arrythmias produced by cyclopropane with a level of anæsthetic depression which is inadequate either for the needs of surgical interference, or for the protection of the subject from the dangers of emotional and/or physical stress. And in clinical practice, when cyclopropane anæsthesia cannot be maintained at the level of complete sensory loss with a regular pulse rate greater than 60 and less than 120 beats per minute, then the subject may be considered unsuitable for cyclopropane. It is the author's practice always to induce with cyclopropane and, if and when the reaction of the particular subject identifies him as an unsuitable subject, to switch immediately to nitrous oxide or ethylene anæsthesia, with di-ethyl or di-vinyl ether if an anæsthetic adjuvant is required.

It can be concluded that the response of healthy subjects to cyclopropane is the standard response if a graduated method of administration is employed. When overpressure is used, either in subjects whose cardiac reserve is impaired or in healthy subjects during cyclopropane anæsthesia deeper than the level of complete sensory loss, a distortion of the standard sequence of response may occur, taking the form of cardiac irregularities which may terminate in primary cardiac failure. This distortion of the standard sequence of response when overpressure is used may be attributed to the sequence of absorption of cyclopropane by the body which in turn is determined by the high oil/water partition coefficient of this anæsthetic.

Trichlorethylene is a heavy, relatively non-volatile anæsthetic fluid with a specific gravity of 1·47 at 15°C and a boiling point of 87°C at mean sea level. Although a potent narcotic, it is a relatively weak anæsthetic, for it exerts a vapour pressure at room temperature of only about 60 mm. of mercury. In clinical practice it is not possible with trichlorethylene to produce loss of tone in the muscles of the trunk sufficient either to perform a laparotomy, or to turn a mal-placed foetus. It is poorly soluble

propane from the heart. It has been said that the cardiac arrythmias of cyclopropane anæsthesia can be abolished by further increasing the partial pressure of cyclopropane in the anæsthetic atmosphere; but if the sequence of absorption of this anæsthetic, as set out in the above discussion, is accepted, then this procedure must be considered dangerous, and, in clinical practice, primary cardiac failure has followed its use. It is clear, too, that while an appropriate concentration of adrenaline may be used with safety as a hæmostatic in healthy subjects during light cyclopropane anæsthesia, its use for any purpose during deep cyclopropane anæsthesia is likely to be followed by ventricular fibrillation.

The evidence discussed indicates that muscular relaxation may be safely produced in healthy subjects with cyclopropane, but since it is a potent anæsthetic gas with a low solubility in blood, overpressure may readily be inadvertently produced with this anæsthetic, and during cyclopropane anæsthesia deeper than the level of complete sensory loss (Guedel's second plane of surgical anæsthesia) overpressure of sufficient intensity will invariably cause cardiac arrythmias which may end in primary cardiac failure, even in a healthy subject. On this account many anæsthetists—and the present writer is one of them—consider it a dangerous practice to push cyclopropane anæsthesia beyond the level of complete sensory loss; when muscular relaxation is required during cyclopropane anæsthesia, these observers employ an anæsthetic adjuvant, such as di-ethyl or di-vinyl ether, or d-tubo-curarine chloride.

In the aged, and in subjects whose cardiac reserve is diminished by pathological change, cardiac irregularities may occur during light cyclopropane anæsthesia. This suggests that the conducting tissue of the heart of such a subject is depressed by a lower concentration of cyclopropane than is the heart of a normal subject. In clinical practice, it is not possible to identify such subjects with certainty before anæsthesia, but pathological change of this character is rapidly revealed by the reaction of the subject early in cyclopropane anæsthesia. In such subjects, bradycardia or tachycardia, with or without cardiac arrythmia, occurs spontaneously early in cyclopropane anæsthesia. As the partial pressure of cyclopropane in the anæsthetic atmosphere is reduced

in the post-anæsthetic period after a long trichlorethylene anæsthetic during which no cardiac irregularities were observed; Condon (1948) has reported just such a case. In the present writer's case, cardiac irregularities were presumed to result from an increase in the trichlorethylene content of the blood sufficient to depress the junctional tissue of the heart, for they followed periods of apnœa during the prolonged recovery from a long trichlorethylene anæsthetic.

The physical properties of trichlorethylene, such as we know them, and its clinical behaviour, are sufficiently like that of cyclopropane to suggest that the sequence of their absorption by the body is similar. But there is one significant difference in the clinical behaviour of these two anæsthetics: for while it is possible by the skilful administration of cyclopropane to produce loss of muscle tone without cardiac arrythmias, with trichlorethylene any attempt to increase the depth of anæsthesia beyond that of complete sensory loss results in cardiac irregularities. This suggests either that the difficulty of avoiding overpressure with the relatively non-volatile trichlorethylene is very great in clinical practice, or that chlorine derivatives (as has long been thought) possess a specific affinity for the conducting tissue of the heart. In the absence of precise information about the physical properties of trichlorethylene, it is perhaps a wise convention to assume that cyclopropane and trichlorethylene are absorbed in the same sequence, for in this instance it is clearly unwise in clinical anæsthetic practice to attempt to push anæsthesia with these two agents beyond the level of complete sensory loss.

Much of the evidence reviewed in this chapter is of a general nature and much of it has been culled from observations directed towards problems other than the problems of anæsthesia. Because of this, arguments and conclusions are of a general rather than of a particular nature and it has been possible to advance probabilities rather than formal proofs. But these probabilities seem to agree so closely with the behaviour observed in clinical anæsthetic practice that they may well be considered as a basis for further investigation. It is clear that the character of the absorption of a given inhalation anæsthetic by the body is determined by the physical properties of the particular anæsthetic, and there is

in water but is freely soluble in fats. (It is used industrially as a de-greaser of metals and a de-waxer of lubricating oils.) Like cyclopropane and chloroform, it is poorly soluble in whole blood. Its oil/water partition coefficient, which has not to date been determined, is without doubt high; When used as an anæsthetic in Man, the pattern of its behaviour indicates an oil/water partition coefficient lying somewhere between that of cyclopropane and chloroform.

Since trichlorethylene is a lipoid-soluble anæsthetic, the standard sequence of response obtains when a graduated method of administration is employed. Because of its physical properties, a slight rise in its partial pressure in inspired air produces an intense biological response, and overpressure may readily be used inadvertently. When overpressure is used inadvertently, and/or when trichlorethylene is employed in a subject whose cardiac reserve is impaired, the response elicited resembles that of cyclopropane rather than that of chloroform.

Thus, if a graduated method of induction is employed, it is observed that cardiac arrythmias do not occur in healthy subjects during light trichlorethylene anæsthesia. Even when overpressure is used with this anæsthetic, to the level of complete sensory loss, cardiac arrythmias are absent, except in subjects whose cardiac reserve is impaired. When however, trichlorethylene anæsthesia is pushed beyond the level of complete sensory loss in healthy subjects, the breathing becomes rapid and alarming cardiac arrythmias follow—without, however, loss of muscle tone in trunk muscles sufficient for the needs of an intra-abdominal surgical procedure. Barnes and Ives (1944) have shown in electro-cardiographic studies of 40 subjects that cardiac arrythmias, such as sinus bradycardia, auricular extrasystoles, and ventricular extrasystoles, occur during trichlorethylene anæsthesia These cardiac arrythmias generally disappear if the partial pressure of trichlorethylene in the anæsthetic atmosphere is immediately reduced to zero and is replaced by an oxygen atmosphere; but, if overpressure is maintained, they may progress to primary cardiac failure, for Lloyd Williams and Hewspear (1942) and Haworth and Duff (1943) have reported two cases of ventricular fibrillation during trichlorethylene anæsthesia. The author has observed that cardiac arrythmias may occur

sequence of response only if a graduated method of administration is employed in clinical practice. Because of their low solubility in whole blood, a graduated method of induction may be a manœuvre of some difficulty, and the control of their partial pressure in inspired air varies as their volatility, being greatest for cyclopropane and least for trichlorethylene. When overpressure is inadvertently used with the members of this group, a distortion of the standard sequence occurs, produced by the absorption of an effective concentration of these anæsthetics by the conducting tissue of the heart. Evidence has been discussed indicating that overpressure is frequently used unwittingly in clinical practice with the members of this group, and that it invariably results in cardiac arrythmias and/or primary cardiac failure. During chloroform anæsthesia, to the difficulty of avoiding overpressure is added the fact that the conducting tissue of the heart reaches full saturation during the stage of non-cooperative stupor, which is, moreover, the period of the greatest secretion of adrenaline; if overpressure is used with chloroform, the conducting tissue of the heart is rendered susceptible to adrenaline at the period of its greatest secretion during anæsthesia. For this reason, chloroform is considered unsuitable for use in clinical anæsthetic practice. If overpressure is unwittingly used with cyclopropane or trichlorethylene, an effective concentration of these anæsthetics is produced in the conducting tissue of the heart of a healthy subject only in anæsthesia deeper than the stage of complete sensory loss, when the secretion of adrenaline is minimal. It follows that they are safe anæsthetics in clinical practice if anæsthesia to the level of complete sensory loss is not exceeded; because cyclopropane is a gas, and trichlorethylene is a relatively non-volatile vapour, overpressure is less likely with the former, for it is more controllable and is a safer anæsthetic in clinical practice than trichlorethylene. When, however, the heart is diseased, its conducting tissue is more susceptible to, and is depressed by a lower concentration of the anæsthetics of this second group than obtains in a normal subject. In such abnormal subjects, the members of this second group of inhalation anæsthetics are contra-indicated in clinical practice. Moreover, Gillespie (1943) with cyclopropane, and Condon (1948) with trichlorethylene, have shown that such subjects are prone to

little doubt that the sequence of absorption of an inhalation ar
thetic by specific areas of functional activity is determined ma
by its physical properties. The olive oil/water partition coeffic
of the anæsthetics discussed is not an absolute measure of
solubility of the anæsthetic in cell lipoids; moreover, these ind
and the lipoid-water content of individual areas of functic
activity and organs need confirmation, but this is held to af
the degree rather than the direction of the relationships invol
It must not be supposed that this is the only factor involve
other factors will be mentioned later—but it does appear to be
dominant factor. There is little doubt, however, that the seque
of absorption of an inhalation anæsthetic by specific areas
functional activity plays a dominant part in determining
biological response of the body to its action, for, once uptake
been affected, fixation and anæsthetic action must follow.

In this light, it can be concluded that the biological respons
the body varies as the physical properties of the particular inh
tion anæsthetic, and that the inhalation anæsthetics in comr
clinical use fall naturally into three broad groups according
their physical properties and to the pattern of their behaviour
clinical anæsthetic practice.

The first group consists of narcotics such as ethyl alcohol a
acetone, whose oil/water partition coefficient is less than unity. T
members of this group exert a dominant action on the brain,
the response produced is not the standard response. They are
suitable for use as anæsthetics in clinical practice because
breadth of therapeutic zone between the depression of specific ar
of functional activity of the brain is narrow and the vital medull
centres are depressed soon after consciousness is lost On t
account, they are so inflexible and difficult to control that they c
be used with safety only when employed in hypnotic doses.

The second group consists of anæsthetics such as cyc
propane, chloroform and trichlorethylene, whose oil/water partit
coefficient is very high; in this discussion all anæsthetics whose c
water partition coefficient is greater than 14 are tentatively inclu
in this group The members of this group in common clinical u
exert a dominant action on the brain and produce the stand

13. MEEK (1908). *Amer. J. Physiol.* 21, 230.
14. MEEK, W. J., HATHAWAY, H. R., and ORTH, O. S. (1937). *J. Pharmacol.* 61, 240.
15. McCOLLUM, J. L. (1930). *J. Pharmacol.* 40, 305.
16. NICLOUX, M., and YOVANOVITCH, A. (1924). *C. R. Soc. Biol. Paris.* 91, 1285.
17. QUASTEL, J. H., and WHEATLEY, A. H. M. (1932). *Proc. roy. Soc. sB.* 112, 60.
18. SOLLMANN, T. (1926). "A Manual of Pharmacology." 6th Ed. p. 334. W. B. Saunders, Co., London.
19. THIENES, C. H., et Al (1941). "Anesthesiology." Nov. 611.
20. WATERS, R. M. (1936). "Lancet." ii, 629.
21. WOOLF, H. G. (1937). "Assoc. Research in Nervous and Mental Dis." 29, 18.
22. WRIGHT, S. (1942). "Applied Physiology." 7th Ed. p. 96, 190. Humphrey Milford, London.

develop cardiovascular complications in the post-anæsthetic period. It must be concluded that the members of this second group of inhalation anæsthetics must be used with great care and clinical acumen, if they are to be used safely.

The third group of inhalation anæsthetics consists of anæsthetics whose oil/water partition coefficient is greater than unity and less than 14. It includes di-ethyl ether, nitrous oxide, acetylene, ethylene and, very likely, di-vinyl ether and ethyl chloride. These anæsthetics produce the standard sequence of response, irrespective of the method of their administration; their only danger is that of anæsthetic overdose, which takes the form of secondary cardiac failure. Since the breadth of therapeutic zone between the depression of the several areas of functional activity of the brain is broad, and because the standard sequence of response always obtains, overpressure is used during their administration, for warning of impending disaster—which takes the form of secondary cardiac failure—is clear cut and predictable. The field of the clinical usefulness of each member of this group is determined by its individual potency. The members of this group are flexible and controllable anæsthetics. Di-ethyl ether, which has an oil/water partition coefficient of 2·3, represents the best compromise in respect to solubility, volatility and potency, and is perhaps the most flexible, the most controllable and the safest inhalation anæsthetic in common clinical use.

References.

1. Bodansky, M (1934) "Introduction to Physiological Chemistry." p 609. 3rd Ed John Wiley & Sons, New York
2. Barnes, C G, and Ives, J (1944) *Proc roy Soc Med* 37, 528.
3. Condon, H A (1948). *Brit med J* ii, 340
4. Eisenhart, C, Simpson, R A, and Gillespie, N E. (1943) *Brit. J. Anæsth* 18, 141
5. Gorodisskay, H (1925) *Biochem Z.* 164, 446
6. Gros, O (1910) *Arch exp Path. Pharmak.* 62, 381
7. Hansen, K (1925). *Skand Arch Physiol* 46, 315.
8. Haworth, J., and Duff, A (1943) *Brit. med J.* i, 381.
9. Lampson, R S, Schaeffer, W C, and Lincoln, J R. (1948) *J. Amer. med Ass* 137, 1575
10. Levy, A G. (1911) "Heart" 3, 99
    (1913) "Heart" 4, 319
    (1912) *Brit med. J.* ii, 627
11. Lloyd-Williams, K. G, and Hewspear, D (1942). *Brit. Med. J.* ii, 170.
12. Macleod, J J. R (1930) "Physiology and Biochemistry in Modern Medicine" 8th Ed. p 170 Henry Kempton, London.

TABLE 34.

THE STANDARD SEQUENCE OF THE DEPRESSION OF THE BRAIN BY BLOOD-BORNE ANÆSTHETICS.

The Standard Sequence of Biological Response			Guedel's Classification (1937)		
Depression of the Higher centres	Amnesia		Stage 1		Analgesia
	Co-operative stupor				
	Non-cooperative stupor		Stage 2		Delirum
	Anæsthetic sleep		Stage 3 (Surgical Anæsthesia)	Plane 1	Sleep
Depression of Areas of Sensory Co-ordination	Loss of the ability to react to external stimulus			Plane 2	Sensory loss
Depression of Areas of Motor Co-ordination	Loss of muscle tone in:	Small muscle groups		Plane 3	Loss of muscle tone
		Large muscle groups			
		Intercostal muscles		Plane 4	Intercostal paralysis
Depression of the Vital Medullary Centres	Failure of the Respiratory centre		Stage 4		Medullary paralysis
	Failure of the Vasomotor centre				
	Failure of the Cardiac centre				

CHAPTER XI

THE CLINICAL SIGNS OF INHALATION ANÆSTHESIA

THE clinical signs of inhalation anæsthesia are the logical consequence of the absorption of an effective concentration of the anæsthetic by specific areas of functional activity of the brain. It is proposed to discuss the clinical signs occurring when these specific areas are depressed in the standard sequence. When the standard sequence of biological response obtains, the specific areas of functional activity of the brain are depressed in the following order:

1. The Higher Centres of the brain.
2. The areas of Sensory Co-ordination of the brain.
3. The areas of Motor Co-ordination of the brain.
4. The vital Medullary Centres:
   - (a) The Respiratory Centre
   - (b) The Vasomotor Centre
   - (c) The Cardiac Centre

This classification, as Table 34 shows, differs only in a minor degree from that of Guedel's well-known classification. The modifications introduced have been thought advisable in order to encourage the anæsthetist to interpret the signs of anæsthesia in terms of the absorption of an effective concentration of the anæsthetic by specific areas of functional activity of the brain, rather than in stages and planes which must be translated back to first principles if the anæsthetist is to understand the import of these clinical signs.

The description of the signs of anæsthesia which follows is that of the standard sequence of biological response; when the particular anæsthetic is correctly administered, it applies alike to all the inhalation anæsthetics, and, in fact, to all blood-borne anæsthetics suitable for use in clinical practice, irrespective of their method of approach to circulating blood.

in all but infants, women in labour, and mental defectives, anæsthetic sleep is invariably approached in a state of apprehension, if not fear, of impending events; in children there may even be a state of intense panic. In modern anæsthetic practice, this emotional state is alleviated or even completely neutralised by the use of appropriate premedication with morphia, scopolamine, barbiturates, etc., and the technique of anæsthetic induction is planned so that every kind of avoidable stimulus—such as touch, pain, pressure and visual and auditory stimulation—is excluded from the subject's person and environment by efficient nursing. In this instance, the subject's reactions during this state of co-operative stupor are almost identical with those of a person preparing for normal sleep, except for a pupil which is smaller than normal when morphia alone is used as a premedicant and a normal or slightly dilated pupil when a balanced dose of atropine or scopolamine is added to this morphia.

When premedication is adequate, nursing efficient and anæsthetic induction swift, the state of co-operative stupor is short, and it merges imperceptibly into the state of non-cooperative stupor which, in the absence of external stimulation, is uneventful. In this instance, stupor is more intense, and volitional control is absent. There is a coarse lateral movement of the eyeball and the pupils, which react to light, are larger than normal. As anæsthesia deepens, this state of stupor passes abruptly to a state of anæsthetic sleep; the most obvious sign of this change is the abrupt alteration of the rhythm of respiration, which becomes regular and mechanical in character.

When, however, premedication is omitted, or is inadequate, and/or when efficient nursing fails to exclude external stimulation during anæsthetic induction, the clinical picture of the state of co-operative and non-cooperative stupor may be modified in a marked degree

In this case, the happy inebriation of the co-operative stupor stage of a properly controlled anæsthetic induction becomes a state of mind that may vary from irrational resentment to uncontrolled panic. Breathing may assume any imaginable type of rhythm, the subject may overbreathe, or he may hold his breath from panic or from a positive purposeful resistance to anæsthetic

The depression of the higher centres of the brain by blood-borne anæsthetics results in the abolition of the higher intellectual faculties of man, together with a gradual inhibition of cortical control. When at length the higher centres have been completely depressed, consciousness is lost. This anæsthetic depression of the higher centres produces the following sequence of events. Conscious memory is lost first, and the subject enters the state of co-operative stupor. With the progressive depression of cortical control as anæsthesia deepens, this state of co-operative stupor gives place to a period of emotional instability termed the stage of non-cooperative stupor which in turn gives place to anæsthetic sleep and with the onset of anæsthetic sleep emotion is completely abolished. The clinical signs of the anæsthetic depression of the higher centres are discussed below in the order of their occurrence, which is.—

1. Amnesia
2. *Co-operative stupor*
3. Non-cooperative stupor
4. Anæsthetic sleep.

In a swift anæsthetic induction, the subject becomes amnesic four to six breaths after exposure to the anæsthetic atmosphere, and with loss of memory enters the state of co-operative stupor. This is a state of happy inebriation when the subject obeys verbal instructions and co-operates with nurses and the anæsthetist, but cerebration is slow.

Co-operative stupor is the level of depression of the central nervous system aimed at when barbiturates or other narcotics are employed for psychiatric abreactions and when nitrous oxide is used to produce dental analgesia. It is often produced by premedication with morphia and/or scopolamine.

The reactions of the subject during this state of co-operative stupor are determined largely by his state of mind just before the commencement of anæsthetic induction and by the nature and intensity of the external stimuli to which he is exposed during this period of time. Natural sleep is approached in an essentially peaceful and relaxed state of mind, and emotional upset is the very antithesis of the normal preparation for sleep. On the other hand,

external stimulation may also slow or even completely arrest a quickened heart by vagal overaction, and subjects with aortic regurgitation are particularly prone to this accident. The response of the subject to emotional and physical stress during this state of non-cooperative stupor is thus characterised by gross autonomic overaction. It is without doubt a period of great danger during anæsthesia, and one when errors or accidents can produce serious, even fatal results. As such, it should be as short as possible. The subject should be guarded from all forms of emotional and physical stimulation by appropriate premedication, efficient nursing and a swift and trouble-free induction. As anæsthesia deepens, even the most stormy period of non-cooperative stupor passes abruptly to the relative safety of anæsthetic sleep and the most characteristic sign of this change of state is the abrupt alteration of the rhythm of breathing, which becomes regular and mechanical in character, and the widely dilated pupils become small again.

When the higher centres of the brain have been completely depressed during anæsthesia, consciousness is lost and a state of anæsthetic sleep occurs. The most important single result of the anæsthetic depression of the higher centres is the fact that from this time onwards in anæsthesia, emotion is abolished and can no longer interfere with the metabolic and physiological activities of the body. This is shown by the pupillary response, for when a state of anæsthetic sleep has been established, the pupil is small and since the areas of sensory co-ordination of the brain are functionally active, the pupil contracts in a reflex manner to light stimulation, but it fails to respond to sympathetic stimulation as shown by its inability to dilate reflexly to adrenaline or external stimulus, and in man, stimulation of the cervical sympathetics produces no measurable exophthalmos. Since sympathetic stimulation ceases with the onset of anæsthetic sleep, and because adrenaline is rapidly oxidised in the body, the results of emotional and physical stress during the non-cooperative stupor stage soon subside and when once regular and mechanical breathing appears, the signs of anæsthetic sleep are almost identical with those of natural sleep.

The clinical picture of anæsthetic sleep is that of an unconscious

induction. Coughing, gagging, glottic spasm, and even vomiting may occur from psychic causes or from appropriate external stimuli. The blood pressure rises and the pulse, which increases in rate, may vary with the phases of his abnormal respiratory effort. The skin is flushed and, owing to psychical or external stimulation, salivary and other glandular secretions increase in volume. The muscles are tense and the subject may struggle so violently as to require manual restraint. The pupils, which react to light, are widely dilated and the upper eyelid is tense and may be retracted, giving the impression of exophthalmos. The whole picture is that of intense sympathetic overaction produced by emotional and physical stress, and asphyxia may be an added factor.

The secretion of adrenaline is regulated by the splanchnic nerves and the autonomic nervous system is to an important extent under the control of the hypothalamus. The activity of the hypothalamus, in turn, is subjected to powerful inhibitory impulses from the cerebral cortex and, as anæsthesia deepens and cortical control is progressively diminished, volition is lost and the subject enters the state of non-cooperative stupor which is also a state of emotional instability when the subject is hypersensitive to all forms of stimuli. In consequence of this, when premedication is inadequate—and particularly if the period of co-operative stupor has been violent—the clinical signs of this state of non-cooperative stupor are dominated by the excessive and exaggerated response of the body to all forms of stimuli, even though the stimuli are of relatively minor intensity. The rhythm and amplitude of breathing is affected by slight degrees of stimulation and coughing, gagging, glottic spasm, and vomiting are readily produced. Salivary, lacrimal, and sweat glands may secrete excessively and the reflex muscular response to comparatively small degrees of visual, auditory and traumatic stimulation may be violent enough to require manual restraint. But, in this state of emotional instability it is the cardiovascular response to relatively minor degrees of stimulation that requires greatest emphasis, for as a result of the excessive secretion of adrenaline, the pulse rate increases and the blood pressure rises: in response to external stimulation, cardiac irregularities with extrasystoles and during chloroform anæsthesia, ventricular fibrillation, may occur. Minor degrees of

concerned with the protection of the larynx, the gag and the cough reflex, are abolished in that order. The eyeballs are now stationary and look straight ahead, the pupils are small and do not now react to light, and the corneal and conjunctival reflexes are abolished. Inspiration and expiration are of equal duration and the rhythm of respiration is regular and mechanical in character. The rhythm and the rate of the heart beat, and the blood pressure, are normal and, at this level of anæsthetic depression, the rhythm of respiration, the blood pressure, and the rhythm and rate of heart beat, are affected only by the most intense proprioceptive stimuli such as violent pulling on the peritoneum or the mesentery, and perhaps by forcible dilatation of the anal sphincter. This is the greatest depth of anæsthesia which it is possible to obtain, after adequate premedication with nitrous oxide in a normal subject when oxygenation is adequate; and it is the greatest depth of anæsthesia which can be produced with trichlorethylene if cardiac arrythmias are to be avoided.

When anæsthesia has reached the level of depression of the areas of sensory co-ordination of the brain, a larger measure of protection is afforded than heretofore, and for the first time since anæsthesia commenced, the subject is freed from the deleterious consequences of the two uncontrollable variables, emotion and external stimulation whose reflex effects upon the body cannot be anticipated either in respect to the intensity or the character of the response which is produced by them. From this time onwards in anæsthesia, and until overdose has depressed the vital medullary centres, the subject reacts only to changes in his internal environment, i.e. in his blood, since the anæsthetist has complete control of the contents of circulating blood, it follows that for the first time since anæsthesia commenced the anæsthetist has complete control of the reactions of his subject. It is the present writer's opinion that surgical interference should not be permitted until anæsthesia to the level of the complete depression of the areas of sensory co-ordination of the brain has been achieved. Reference to Table 34 shows that his opinion is at variance with that of Guedel, for in Guedel's classification the third stage of anæsthesia is termed the stage of surgical anæsthesia, and the first plane of this stage is seen to be that of anæsthetic sleep.

subject whose areas of sensory co-ordination respond sluggishly to external stimulation and whose areas of motor co-ordination and vital medullary centres are intact and active although voluntary movement is no longer possible. The metabolic rate is diminished and in keeping with this fall in the metabolic rate and because emotion has ceased to act, cardiac output is decreased, the pulse rate slows and cutaneous vasodilatation occurs. The minute volume of lung ventilation is diminished, the depth of breathing decreases and a compensatory increase in the rate of respiration occurs. Inspiration and expiration are of approximately equal duration, and respiration takes on a regular mechanical rhythm which can be modified only by external stimulation of considerable intensity. Voluntary movement is, of course, abolished and striated muscles, in the absence of external stimulation, are flaccid, but muscular movements of a reflex nature are possible, although the threshold of stimulus necessary to produce reflex action is greater than normal. The vomiting, swallowing, pharyngeal and laryngeal reflexes are present, though they are sluggish in their response to stimulus and the lacrimal, salivary, and bronchial glands secrete, though with diminished volume. There is a fine, slow, lateral movement of the eyeballs. The pupil is small and it contracts to light and all other protective reflexes of the eye react to external stimulus, but the pupil fails to dilate reflexly in this state of anæsthesia The level of depression of the brain desired when avertin, paraldehyde, or the barbiturates are used to produce basal narcosis is that of anæsthetic sleep, for the aim of basal narcosis is to protect from emotion while at the same time retaining all the benefits of the physiological protective reflexes.

In the standard sequence of the biological response of the body to blood-borne anæsthetics, the areas of sensory co-ordination of the brain are next depressed and the body then fails to react in a reflex manner to external stimulus. Skin sensation is abolished in the order, the back, the extremities, the genitalia, and the face. Muscular movement of a reflex nature is no longer possible, and the muscles are flaccid, but do not lose their tone. Since external stimulation is no longer able to activate them, the lacrimal, salivary and bronchial glands cease to secrete, and for the same reason, the vomiting and the swallowing reflexes and the reflexes

signs of anæsthesia during the depression of the higher centres, for he aims to pass through this period of anæsthetic induction with the utmost celerity. His very real concern is to determine when anæsthesia to the level of depression of the areas of sensory co-ordination of the brain has been reached, for here is a zone of relative safety; at this point, too, overpressure must be reduced and haste made more slowly. The significant signs of anæsthesia at the level of the complete depression of the areas of sensory co-ordination of the brain are seen to result from the inability to react to external stimulation and all that this implies.

When the standard sequence of biological response obtains, as anæsthesia deepens beyond the level of the complete depression of the areas of sensory co-ordination of the brain, the areas of motor co-ordination of the brain and then the vital medullary centres are successively depressed. (Table 34.) The clinical signs of anæsthesia during this period can, therefore, be divided into two groups of signs. The first group of signs, common to all degrees of anæsthetic depression beyond this point, can be termed " negative " signs, for they result from the inability of the subject to react in a reflex manner to external stimulation. In the second group, the signs, which may be termed " positive " signs, vary as the depth of anæsthesia and they are produced by the progressive loss of muscle tone in specific groups of muscle as anæsthesia deepens. Table 35, which is an amplification of the information in Table 34, shows that during this period of anæsthesia the musculature of the body becomes atonic; the table brings out the fact that particular muscle groups lose their tone in a precise and characteristic order when the standard sequence of biological response obtains. And it is proposed briefly to recapitulate the negative signs of anæsthesia during this period and to describe the positive signs of anæsthesia in terms of the progressive loss of muscle tone in specific groups of muscles, for an efficient anæsthetic preparation for a given type of surgical procedure depends essentially upon the degree of muscular relaxation required

During this period of anæsthesia, because of the inability of the subject to react in a reflex manner to external stimulation, the pupils do not react to light and the surface of the conjunctiva

In recent years, amongst some anæsthetists at least, the vogue of light anæsthesia during surgical interference has been carried to extremes in the interest of a minimum degree of post-anæsthetic metabolic upset, and this is so particularly since the introduction of curare as a means of producing muscular relaxation. There is little doubt that the intensity of post-anæsthetic metabolic upset bears a definite relationship to the depth and duration of anæsthesia (see page 494); but if this consideration is allowed to determine too light anæsthesia, and if other factors—emotional and physical stress and the effect of external stimulation—are ignored, then deleterious reflex effects are introduced which may endanger the life of the subject. In simplest terms, the responsibility of the anæsthetist to his patient is threefold: he must produce a suitable operative field for his surgeon, he must achieve this end with the greatest possible protection of his patient, and, finally, these two essentials must be fulfilled with the smallest possible degree of post-anæsthetic metabolic upset. Light anæsthesia seldom fulfills the first condition, and, in the writer's opinion, a level of anæsthesia less than the complete depression of the areas of sensory co-ordination of the brain never satisfies the second condition. To fail to comply with these two essentials is to fail indeed. The anoxia and/or the surgical trauma etc., which are associated with an ineffective anæsthetic preparation, increase the intensity of post-anæsthetic metabolic upset in spite of the light level of anæsthetic depression produced; equally, lack of protection from the reflex effects of emotion and/or external stimulation may endanger the life of the subject.

If the premise is sound—that surgical interference is not to be permitted until a state of anæsthesia to the level of the complete depression of the areas of sensory co-ordination of the brain has been established—then the protection afforded by a swift induction to the level of loss of the ability to react to external stimulation should be the aim of the anæsthetist in every anæsthetic. This aim can be achieved with adequate premedication and the intravenous barbiturates, or with basal narcosis followed by a swift anæsthetic induction with inhalation anæsthetics based on the methods of control already suggested and which are to be discussed in detail later. In this instance the anæsthetist is not concerned with the

co-ordination of the brain, for muscular relaxation is seldom needed and the inability of the subject to react to external stimulus results in a flaccidity of the muscles which is sufficient to permit many types of extra-abdominal operations to be performed. Moreover, very soon after this level of anæsthetic depression has been achieved—and with no material change in the clinical signs of anæsthesia—muscle tone is lost in small muscle groups such as the forearm and hand, the leg and the foot, etc., and this degree of muscular relaxation is sufficient to provide an efficient anæsthetic preparation for most extra-abdominal operations. When pre-medication is adequate it is generally possible to achieve this level of anæsthetic depression safely with nitrous oxide and with trichlorethylene.

In all intra-abdominal operations, and in a limited number of extra-abdominal surgical procedures, complete muscular relaxation —that is, loss of muscle tone equivalent to a complete lower motor lesion of the muscles concerned—is a necessary condition for the production of a suitable operative field. In clinical anæsthetic practice it is customary to divide intra-abdominal operations into two groups, viz. lower and upper abdominal operations. It is convenient, therefore, to consider the clinical signs accompanying muscular relaxation in large muscle groups in two sequence of events; first, the signs which occur with the complete loss of tone in the lower abdominal musculature; and, second, the signs which accompany the complete loss of muscle tone in the upper abdominal musculature. This order of loss of muscle tone coincides with the sequence of the anæsthetic depression of the relevant areas of motor co-ordination of the brain.

Loss of muscle tone in the lower abdominal muscles is achieved an appreciable time after sensory loss is complete. Owing to the relaxation of the lower abdominal muscles, the lower intercostal muscles tend to lag on inspiration and breathing tends to assume a costal character. The rhythm of respiration is regular, expiration tends to be more prolonged than inspiration, and this prolongation of expiration is emphasised when positive pressure is used. Breathing is more rapid than in normal conditions of life and its amplitude is decreased Shallow breathing and relaxed abdominal muscles tend to interfere with the efficient return of venous blood

TABLE 35.

THE STANDARD SEQUENCE OF LOSS OF MUSCLE TONE DURING BLOOD-BORNE ANÆSTHESIA

Anæsthetic Depression of		Loss of Muscle Tone in
Areas of Motor Co-ordination		1. Small muscle group of striated muscle.
		2. Large muscle groups. Lower abdominal musculature and smooth muscle of hollow visci.
		3. Large muscle groups· Upper abdominal musculature and sphincters.
		4. Intercostal muscles and sternocostal part of the diaphragm.
Vital Medullary Centres	(a) Respiratory centre	5 Crural part of the diaphragm
	(b) Vasomotor centre	6 Smooth muscle of the blood vessels
	(c) Cardiac centre	7 Heart muscle

tends to lose its moist appearance, for tears are not secreted and, moreover, the conjunctival reflex no longer protects the surface of the eye The sweat glands do not secrete and the skin becomes less moist The salivary and the bronchial glands do not secrete; excessive secretions which may have accumulated in the lungs during anæsthetic induction soon evaporate, and the pulmonary system, in the absence of circulatory failure, remains dry throughout. The cough reflex is abolished and does not now protect the pulmonary system. The rhythm and the rate of heart-beat, the blood pressure and the rhythm of respiration are not influenced during this period of anæsthesia by nociceptive stimulation the subject is, in effect, a standard physiological preparation, for he reacts only to alterations in his internal environment, his blood.

Many extra-abdominal operations may be performed at the level of the anæsthetic depression of the areas of sensory

of relatively short duration, as evidenced by the blood pressure and pulse rate. With the prolongation of this set of circumstances, however, a real embarrassment of the cardiovascular system eventually becomes apparent, for the pulse rate rises, the blood pressure falls, and a greater partial pressure of oxygen in the atmosphere breathed is required adequately to oxygenate the subject; with the onset of these symptoms, fatal cardiac failure will rapidly occur, unless intravenous fluids (preferably whole blood) are quickly administered.

It is seen that the response of the respiratory and the cardiovascular systems to the progressive loss of muscle tone in large muscle groups provides precise and characteristic information of the level of anæsthetic depression; to this may be added the reaction of the pupils during this period of anæsthesia. It has been seen that the reaction of the eye muscles gives accurate information of the anæsthetic depression of the higher centres and the areas of sensory co-ordination of the brain. The reaction of the eye muscles also affords accurate information of the progressive depression of the areas of motor co-ordination during blood-borne anæsthesia. When complete sensory loss has been established, the extrinsic muscles of the eyeball no longer react to external stimulation, but they are tonic and in balanced equilibrium and the eyeball looks straight ahead As deepening anæsthesia abolishes muscle tone in these muscles, which are in balance, the position of the eyeball remains unaltered.[1] When sensory loss is complete, the intrinsic muscles of the eye, being unable now to dilate or constrict the pupil reflexly, are tonic but are not in balance, for the more powerful constrictor, as is usual, overcomes the weaker dilator: the result is small pupils which do not react to light. As deepening anæsthesia reduces the tone of both muscles, the pupils dilate passively, owing to the recoil of the elastic fibres of the completely atonic iris, in the same manner seen in post-mortem dilatation of the pupils. In clinical practice, the degree of dilatation of pupils which do not react to light is an accurate

[1] When a squint is present, the extrinsic muscles of the eyeball are not in balance, during anæsthesia the eyeball does not look straight ahead, and the squint persists

to the right heart, and, if abdominal section has been performed, the support afforded to the great vessels is further diminished. The efficiency of the cardiovascular system at this depth of anæsthesia is, *however, seldom impaired in a healthy* subject, unless anæsthesia is prolonged for an unwarranted period of time; but, in such a case, the cardiac output is diminished, the blood pressure tends to fall and the pulse rate tends to increase. This is the greatest depth of anæsthesia which it is possible to attain in a normal subject with adequate premedication when ethylene or acetylene is used, and it is the greatest depth of anæsthesia that many anæsthetists think safe to produce when cyclopropane alone is used.

As anæsthesia deepens, loss of muscle tone is produced in the upper abdominal muscles and finally in the intercostal muscles and the sternocostal part of the diaphragm. Consequently, breathing gradually diminishes in amplitude and may increase in rate, with obvious prolongation of expiration, but its rhythm remains regular. As loss of muscle tone involves the intercostal muscles and the sternocostal part of the diaphragm, this shallow rapid breathing *gives place to short, jerky, shallow inspirations, and a tracheal tug* makes its appearance. Inspiration terminates suddenly and the chest collapses, by virtue of the elastic recoil of the costal cartilages and the elasticity of the lungs, to the position of expiration; this type of breathing, with or without a tracheal tug, is indicative of dangerously deep anæsthesia, and is the precursor of respiratory failure.

As anæsthesia deepens, too, the diminished intra-abdominal pressure produced by the progressive relaxation of the abdominal musculature combines with abdominal section to hinder the return of venous blood to the thorax and, as breathing becomes shallower, the diminished negative intrapleural pressure further impedes venous return These factors combine to reduce the venous return to the right heart and, as anæsthesia deepens, to reduce progressively the cardiac output and the blood pressure tends to fall and the pulse rate tends to increase On the other hand, as anæsthesia deepens, the metabolic rate of the body is progressively diminished and, if anoxia is avoided, it is surprising to note how little embarrassment of the cardiovascular system occurs in a deep anæsthesia

identical with that of di-ethyl ether, but clinical experience indicates that respiratory failure follows more rapidly on a widely dilated pupil with this anæsthetic than is the case with di-ethyl ether.

During cyclopropane, and especially during chloroform anæsthesia, a dilated pupil spells very great danger. On the one hand, a dilated pupil which reacts to light indicates that the subject is exposed to the deleterious effects of emotional stimulation, which in the case of chloroform may result in primary cardiac failure. On the other hand, a dilated pupil which does not react to light during cyclopropane or chloroform anæsthesia indicates overdose with incipient depression of the vital medullary centres. The greatest depth of anæsthesia which the skilled chloroformist of the past thought safe to produce was indicated by a pupil not reacting to light, which was described as " coming and going," for as soon as the passive dilatation of the pupil commenced, this dilatation was checked by the withdrawal of chloroform, after which the concentration of chloroform in the anæsthetic atmosphere was cautiously increased, only to be checked again when the pupil commenced to dilate. Relative to di-ethyl ether, the breadth of therapeutic zone between the depression of the areas of motor co-ordination of the brain and the vital medullary centres is small with cyclopropane and chloroform. This can be attributed partly to their low solubility in whole blood, which determines that even a small increase in the partial pressure of these anæsthetics in the anæsthetic atmosphere is immediately reflected in the anæsthetic contents of circulating blood, and partly to their narcotic potency, which ensures that a relatively small increase in the tension of these anæsthetics in circulating blood is followed by a comparatively intense depression of the cells of the nervous system.

When scopolamine and/or morphia are used as premedicants it is sometimes difficult with potent anæsthetics, such as di-ethyl ether, to produce passive dilatation of the pupil as rapidly as the rate of absorption of the anæsthetic by the body would lead one to expect, and the dilatation of the pupil lags behind the loss of muscle tone in large muscle groups. This may be due to the slower absorption of inhalation anæsthetics when heavy premedication with these narcotics is used. Morphia, however, has an affinity

measure of the degree of muscular relaxation of large muscle groups.[1]

Nitrous oxide, ethylene, acetylene and trichlorethylene are none of them sufficiently potent, however, to produce anæsthesia to the level of complete depression of the areas of motor co-ordination of the brain; in the presence of adequate oxygenation, it is impossible with these inhalation anæsthetics to produce passive dilatation in a pupil which does not react to light. And dilatation of the pupil with these anæsthetics spells danger; for, if it occurs in a pupil which reacts to light, the deleterious effects of emotion are acting. Occurrence in a pupil which does not react to light indicates, in the case of nitrous oxide, ethylene and acetylene, that anoxia is acting and the early failure of the vital medullary centres can be anticipated, in the case of trichlorethylene, cardiac arrythmias occur before or soon after the pupil commences to dilate. It follows, during anæsthetic maintenance with nitrous oxide, ethylene, acetylene, and trichlorethylene, that the pupil should always be small.

When di-ethyl ether is used alone, or as an adjuvant to any of the inhalation anæsthetics in common clinical use (and this excludes chloroform) the passive dilatation of the pupil indicates the anæsthetic depression of the areas of motor co-ordination of the brain and, in turn, loss of muscle tone in large muscle groups. A moderately dilated pupil which does not react to light indicates loss of muscle tone in the lower abdominal musculature, and, when such a pupil is widely dilated, the upper abdominal musculature is atonic, while extreme dilatation with a tracheal tug denotes that in addition the intercostal muscles and the sternocostal part of the diaphragm have lost their muscle tone. Although a widely dilated pupil not reacting to light denotes a state of anæsthesia just short of failure of the respiratory centre, this level of anæsthetic depression can be safely produced with di-ethyl ether if anoxia is avoided, for the absorption and excretion of di-ethyl ether are rapid and freely controllable, its biological response is always the standard one, and its therapeutic zone is broad.

The reaction of the pupil during di-vinyl ether anæsthesia is

[1] Pathological conditions of the iris may prevent the reflex constriction and/or the passive dilatation of one or both pupils

breathing; inspiration and expiration begin and end suddenly, and this unit respiratory effort is followed by a pause of about five seconds and more. This gives way after a few irregular gasps to the cessation of all diaphragmatic action, and breathing ceases. This sequence is combined with cyanosis and all the signs of oxygen lack. The conjunctiva is dry and glazed, and the pupils, which do not react to light, are fully dilated; the blood pressure is low and the pulse is rapid, thin and thready.

Meanwhile the vasomotor centre, which is situated in the floor of the fourth ventricle at the level of the apex of the calamis scriptorius, is at first stimulated through the chemo-receptors in the arch of the aorta and the carotid body, by the excess of carbon dioxide and oxygen lack caused by respiratory failure, and the smooth muscle of the arterioles contracts with consequent slight rise of blood pressure. This, however, is quickly followed by loss of muscle tone in the smooth muscles of arterioles; the capillary response, which will have long been sluggish, now disappears; peripheral resistance is abolished, and the blood pressure falls to zero.

Finally, as an end result, the cardiac centre (which is believed to be situated in the floor of the fourth ventricle adjacent to the vagus nucleus) is completely depressed by anæsthetic overdose and anoxia, and the cardiac output—which has been progressively falling as venous return diminishes—is reduced to zero, and the myocardium becomes toneless and ceases to contract.

The clinical signs of blood-borne anæsthesia are thus seen to be the logical consequence of the orderly depression of the functional activity of specific areas of the brain. In terms of the character and the sequence of functional loss, blood-borne anæsthesia may be described in three successive phases, which are:—

1. Depression of Emotional Activity.
2. Depression of Sensation.
3. Depression of Motor Tone.

The first phase is the period of greatest danger during anæsthesia. The excessive and exaggerated response of the body to emotional stress colours the whole picture; but, when emotion has been abolished, a period of relative safety is reached.

The second phase is a period of relative safety when the

for the specific area of motor co-ordination concerned with the intrinsic muscles of the eye; it produces a pin-point pupil which Clark (1940) says is due to the direct stimulation of the oculomotor centre by morphia. And it is possible that this lag in the dilatation of the pupil, followed by a relatively sudden dilatation, results from the adsorption displacement of morphia from the site of its drug fixation in this specific area of motor co-ordination by di-ethyl ether when at length a certain critical concentration has been attained in the cells of the area. In this instance, the size of the pupil before dilatation suddenly occurs is not an accurate measure of the loss of muscle tone in large muscle groups, and the inexperienced anæsthetist may be misled unless he is very attentive.

When, through errors or accidents of administration, the concentration of a blood-borne anæsthetic in the brain exceeds the threshold concentration necessary to completely depress the areas of motor co-ordination of the brain, anæsthetic overdose is present; as the concentration of the anæsthetic gradually rises, the vital medullary centres are depressed in the following order: the respiratory centre fails first, then the vasomotor centre and, as an end result, the cardiac centre fails.

The first sign of serious threat to the vital medullary centres is, therefore, the inability of diaphragmatic breathing to oxygenate the subject adequately, and when the respiratory centre is completely depressed, breathing ceases The grey matter which controls respiratory activity is probably situated in the pons and upper part of the medulla, and Lumsden (1923) has shown that breathing changes in a characteristic fashion when this centre, or series of centres, is progressively depressed. The rapid, shallow, jerky, regular breathing with a tracheal tug—which denotes relaxation of the intercostal muscles and the sternocostal part of the diaphragm—changes as anæsthesia deepens to apneustic breathing, which has been described as " apnœa in inspiration " A slow deep inspiration is followed by a characteristic pause in the inspiratory position which may be maintained for as long as two to three minutes, this prolonged inspiration is followed by a sudden relaxation of the inspiratory muscles, and the thorax suddenly returns to the expiratory position The cycle is then repeated. Apneustic breathing in turn gives way to gasping

CHAPTER XII

THE MODE OF EXCRETION OF INHALATION ANÆSTHETICS AND THE CLINICAL SIGNS OF ANÆSTHETIC RECOVERY

INHALATION anæsthetics, being non-reactive gases and vapours, are excreted from the body by the lungs, unchanged and in the same form as that in which they were absorbed. The mechanism of their excretion from the body is a recapitulation, in the reverse direction, of their absorption by the body. As soon as anæsthetic administration ceases and the partial pressure of the anæsthetic in inspired air falls to zero, anæsthetic gases and vapours move by diffusion and the mass movement of circulating blood and lung ventilation, from the region of highest pressure (the body) to the region of lowest pressure (atmospheric air). Excretion is exponential in character and is rapid until 50 per cent. of the absorbed anæsthetic has been excreted; excretion then slows very appreciably as the diffusion gradient of the anæsthetic gradually decreases in a logarithmic manner. The rate at which a particular anæsthetic is excreted from the body depends upon the mass of anæsthetic to be excreted, that is, the absorptive capacity of the body for that anæsthetic on the one hand, and, on the other hand, the carrying capacity of one round of blood for that anæsthetic. This ratio will be recognised as the absorption coefficient, or as it will now be termed, the " excretion coefficient " of the body for the particular anæsthetic, and the rate of excretion of the inhalation anæsthetics in common clinical use is of the same order as the rate of their absorption by the body.

The rate of excretion of a given inhalation anæsthetic depends upon its excretion coefficient, its diffusion gradient as between the body and atmospheric air, and the presence of effective mass movement of the anæsthetic by circulating blood and lung ...tion. Nothing analagous to overpressure can be used to

exaggerated response of normally protective reflexes may introduce an element of danger. When at length the ability to react to external stimulation is abolished a period of safety is reached. For reasons already given, the author considers these first two phases *to be the period of anæsthetic induction.*

In the third phase, neither emotion nor external stimulus can affect the subject. But the absence of muscle movement, the loss of muscle tone in large muscle groups, and the lessened negative intrapleural pressure combine to diminish eventually the return of venous blood to the right heart, and in turn the output of the heart. Diminished cardiac output next produces the vicious circle of fall of blood pressure and anoxia. Cardiovascular distress of this origin is produced more rapidly in a subject with hyperpiesis than in a normal subject and the speed with which it occurs depends upon the depth and duration of anæsthesia. In the author's opinion cardiovascular distress of this origin has not received sufficient emphasis in anæsthetic literature.

REFERENCES.

1. CLARK, A. J (1940). "Applied Pharmacology." *7th Ed. p.* 251 J. & A. Churchill Ltd., London.
2 GUEDEL, A. E, (1937). "Inhalation Anesthesia" p. 14. The Macmillan Company, New York
3 LUMSDEN, T (1923) *J. Physiol.* 57, 153, 345

than that of organs such as subcutaneous fat, which will consequently lose anæsthetic to circulating blood. It is clear that the tension of the inhalation anæsthetic in any organ or area of functional activity cannot fall materially below that of arterial blood flowing through the organ, except for very short periods of time; and the ability of any organ or area of functional activity of the body to de-saturate rapidly or slowly is not, *per se*, a decisive factor in determining the rate of the excretion of inhalation anæsthetics.

The maximum excretory rate of inhalation anæsthetics from any organ or area of functional activity is, therefore, conditioned by the rate of excretion of the anæsthetic by the body taken as a whole, and it follows that the rate of excretion by the body taken as a whole combines with the individual susceptibility of specific areas of functional activity of the nervous system to narcotics, to determine the sequence of recovery of the body from the depressing effect of an inhalation anæsthetic.

Suppose that anæsthesia has been carried to the level of depression of the respiratory centre without anoxia. As de-saturation of the body taken as a whole proceeds, the concentration of the inhalation anæsthetic in arterial blood and in turn the brain first falls below the minimum threshold concentration necessary to depress the cells of the respiratory centre, whose functional activity then returns. Next, the concentration of the anæsthetic in arterial blood and in turn the brain falls below the threshold concentration necessary to depress the areas of motor co-ordination of the brain, and muscle tone returns in the reverse order of its abolition during induction. The concentration of the anæsthetic in arterial blood and in the brain then falls below the threshold concentration necessary to depress the areas of sensory co-ordination of the brain, and the ability to react in a reflex manner to external stimulus returns. Finally, the concentration of the inhalation anæsthetic in arterial blood and in the brain falls below the threshold concentration necessary to depress the higher centres of the brain; and although de-saturation of the body is not yet complete, the functional activity of the higher centres returns to normal, and anæsthetic recovery is complete.

Thus, the rate of recovery from inhalation anæsthesia varies as

hasten the excretion of an inhalation anæsthetic from the body; for, when anæsthesia ceases the diffusion gradient is then at its greatest value and decreases progressively and in a logarithmic manner as excretion proceeds. Of these factors, only the minute volume of lung ventilation can be wittingly increased in the interest of more rapid excretion, but shallow breathing and a reduced circulatory rate prolong the excretion time of inhalation anæsthetics. The therapeutic use of carbon dioxide in inspired air increases the rate of excretion of inhalation anæsthetics, but its usefulness in this respect is conditioned by the solubility of the particular inhalation anæsthetic in whole blood. Deep breathing produces a very material increase in the excretory rate of anæsthetics (such as di-ethyl ether) which are very soluble in whole blood, but only an insignificant increase over the normal rate of excretion can be expected with anæsthetics such as cyclopropane, chloroform and trichlorethylene, which are poorly soluble in whole blood. It is clear that the rate and character of the excretion of inhalation anæsthetics from the body are determined by the physical properties of the particular inhalation anæsthetic.

At the first round of blood after administration ceases, mixed venous blood in gaseous equilibrium with the average tension of the inhalation anæsthetic in the body taken as a whole, returns to the pulmonary capillaries; because of the anæsthetic lost to alveolar air—and in turn excreted from the body—blood leaving the pulmonary capillaries on the second round after anæsthetic administration ceases, contains the anæsthetic at a tension lower than that of the average tension of the body taken as a whole. The tension of the inhalation anæsthetic in arterial blood of this second round may be equal to or greater than that of organs such as the brain, the kidneys and the heart, which have the ability to excrete rapidly. It will be lower than that of organs such as subcutaneous fat, whose rate of excretion is slow, but is always less than that of the body taken as a whole. If perchance the tension of the anæsthetic in arterial blood of this second round is greater than that of an organ such as the brain, anæsthetic would be absorbed by the organ and the excretion of the anæsthetic from this organ would temporarily cease. On the other hand, the tension of anæsthetic in arterial blood of this second round is less

occur. The clinical signs of recovery from threatened or established secondary respiratory failure are so bound up with the treatment of this condition, that it is difficult to describe the one without the other. When respiratory failure is present or is suspected during inhalation anæsthesia, the following measures are immediately put into operation. The subject is placed in the Trendelenburg position, his airway is cleared, the anæsthetic atmosphere is replaced by an oxygen atmosphere and artificial respiration is begun. In this instance, the posture adopted increases the venous return to the right heart. Since the mass movement of respiratory and anæsthetic gases and vapours by circulatory blood is still possible, anæsthetic gases and vapours and carbon dioxide, on the one hand, must move from the region of higher pressure (the body) to the region of lower pressure (the oxygen atmosphere); on the other hand, oxygen must move from the oxygen atmosphere to the brain, to the vital medullary centres and to other tissue cells of the body. Since, moreover, the diffusion gradient of both oxygen and the inhalation anæsthetic is high, it follows that their diffusion velocity is rapid, and as long as effective artificial respiration is continued and circulatory depression does not increase from any other reason, the rapid oxygenation of the subject and the rapid excretion of the inhalation anæsthetic and carbon dioxide must occur. In this manner, the concentration of the inhalation anæsthetic is rapidly reduced below the minimum threshold concentration necessary to depress the vital medullary centres, and the vicious circle—fall of blood pressure and oxygen lack—is rapidly broken. As a result, the blood pressure rises, the capillary response to pressure returns, a bright pink colour replaces the dusky cyanosis, and soon afterwards spontaneous breathing recommences. Cessation of breathing during anæsthesia is not, *per se*, a calamity if an effective circulation is still present, for the mass movement of lung ventilation can be replaced by effective artificial respiration. The popular press tells of a Californian who has lived for the past 15 years and more in an iron lung, and during this time has not only married a wife but has also produced a family.

The cessation of the mass movement of respiratory gases and vapours by circulating blood, however, is the greatest calamity

the excretion coefficient of the body for the particular inhalation anæsthetic. The character and the sequence of anæsthetic recovery is the same for all the inhalation anæsthetics in common clinical use and is determined by the individual susceptibility of specific areas of functional activity of the brain to narcotics. It is a recapitulation in the reverse direction of the standard sequence of response of the body to inhalation anæsthetics.

The clinical signs which occur during recovery are the logical consequence of this sequence of excretion. If anæsthesia has been carried to the level of depression of the vital medullary centres, and if appropriate treatment of this condition has been promptly instituted, the order of recovery of specific areas of functional activity of the brain is as follows:

1. The Vital Medullary centres.
2. The Areas of Motor co-ordination of the brain.
3. The Areas of Sensory co-ordination of the brain.
4. The Higher centres of the brain.

When the sequence of biological response of the body to an inhalation anæsthetic is the standard one, and if overdose is permitted to develop unchecked, the respiratory centre eventually fails and breathing ceases; but at this point the vasomotor centre and the cardiac centre, although depressed, continue to function and a circulation is still present In untreated cases, oxygen lack and the progressive increase of the concentration of the anæsthetic in the vasomotor and the cardiac centres, soon produce complete loss of peripheral resistance· the blood pressure rapidly falls, and cardiac arrest occurs in one to five minutes after breathing has ceased The clinical signs of depression of the respiratory centre are so distinct and characteristic that it is unlikely that overdose with inhalation anæsthetics ever exceeds the concentration necessary to depress the respiratory centre; when death occurs from secondary cardiac failure during inhalation anæsthesia, it is probable that the anoxic factor is almost invariably responsible for the terminal event If, however, oxygen lack is arrested before the effectiveness of the circulation is seriously impaired, and if ways and means are provided to excrete the excess of anæsthetic rapidly from the vital medullary centres, then, in the absence of other factors, complete recovery of the respiratory centre will rapidly

drugs are not antidotes to narcotics, for they do not destroy or hasten the destruction or excretion of narcotics.[1] They are adjuvants to and not substitutes for posture, a clear airway, artificial respiration with an oxygen atmosphere and intravenous fluids. If syncope still persists after 60 seconds, in spite of these measures and in spite of manual rhythmic pressure on the chest wall, an intracardial injection should then be given. When chloroform, cyclopropane or trichlorethylene is the anæsthetic responsible for syncope, the intracardial injection should consist of atropine, but adrenaline should on no account be used. When any of the remaining anæsthetics in common clinical use is responsible, the intracardial injection may consist of adrenaline or any one of the analeptic drugs already mentioned. If this rather dramatic form of treatment has produced no effect within 60 seconds, manual cardiac massage must be instituted. To be of any immediate and lasting benefit, cardiac massage must be commenced within about three minutes of the onset of syncope. Manual cardiac massage alone is quite useless when the cause of syncope is found to be due to ventricular fibrillation of the heart,[2] but when the myocardium is found to be inert it will often be possible by this means to recommence heart action. When ventricular fibrillation is found to be present the inco-ordinate contractions of the fibres of the myocardium may be stopped by the intracardial injection of 10 c.c. of a 1 per cent. solution of procaine, and it may then be possible to re-commence the co-ordinate heart action by rhythmic manual pressure.

Hamilton Bailey's report (1941) of about 40 cases of cardiac massage suggests that syncope during anæsthesia, with the cardiac massage which it often necessitates, is a relatively common occurrence in anæsthetic practice. This suggestion is not just: in

[1] The increased depth of breathing and the cough following the intravenous injection of a large dose of coramine, picrotoxin, etc. is not a measure of anæsthetic recovery These signs are due to stimulation of the vital medullary centres and/or the carotid body and are reflex acts. In the convulsion therapy of schizophrenia with analeptic drugs, this medullary stimulation is looked upon as the pre-convulsion stage of the injection

[2] In a ventricular fibrillation during chloroform anæsthesia, I observed during manual cardiac massage that the ventricle continued to fibrillate for 57 minutes after cardiac massage had commenced —T.A.B H

that can occur during anæsthesia, and unless an effective circulation can be re-established within a period of time which has been arbitrarily fixed at three to five minutes, death of the subject is inevitable, for there is no possible substitute for the mass movement of respiratory gases and vapours by circulating blood.

During anæsthesia, circulatory failure may be produced by the deficient venous return caused by loss of muscle tone in large muscle groups maintained for too long, or it may result from anæsthetic overdose. In the first case, warning of impending disaster is clear and definite, and the progress of incipient circulatory failure can be checked by the administration of intravenous fluids, preferably whole blood. In the second case, warning of secondary cardiac failure is equally clear, for the respiratory centre fails before the vasomotor and the cardiac centres, and steps can be taken to check the progress of incipient secondary cardiac failure or to treat it when it has become an established fact.

The treatment of circulatory distress during anæsthesia, irrespective of its cause, has as its immediate object the support of the cardiovascular system by the relief of anoxia and the augmentation of cardiac output by increasing the venous return to the right heart This is effected in the following manner. The subject is immediately placed in the Trendelenburg position, the airway is cleared, and artificial respiration with an oxygen atmosphere at a positive pressure of 5-10 mm. of mercury is begun. If a circulation is still present, manual rhythmic pressure on the anæsthetic reservoir is sufficient; but if the circulation is very feeble or has ceased, manual rhythmic pressure on the chest wall is essential, *for this increases the venous return to the right heart and is* in addition a form of cardiac massage. These measures may be supplemented by the injection of epinephrin, strychnine, caffeine. camphor, coramine, cardiazol, picrotoxin, lobeline, etc. These drugs stimulate the vital medullary centres and/or the carotid body, and by increasing cardiac output produce a rise of blood pressure. Their use in circulatory failure may be the means of maintaining the circulation during the time necessary for lasting relief to be obtained by the abolition of the anoxic factor and the excretion of excess of anæsthetic from the vital medullary centres in the manner set out above It must be emphasised that these analeptic

of carbon dioxide to inspired air may be necessary to re-start the activity of an otherwise functionally active respiratory centre.

The first respiratory effort consists of a series of isolated gasps, which are followed, as recovery proceeds, by prolonged inspirations interspaced with gasps, which in turn give place to apneustic breathing. This is quickly replaced by shallow jerky inspirations with prolonged expirations; almost at the same time a tracheal tug makes its appearance, indicating that the crural part of the diaphragm has recovered its full function. At this stage of recovery the pupil is still widely dilated, but the surface of the conjunctiva has lost its glazed, lifeless appearance. The blood pressure has risen to within the limits of normality, the capillary response to pressure is brisk and the pulse, which is full and regular, may even have fallen to about 100 beats per minute.

As the excretion of the inhalation anæsthetic proceeds, the concentration of the anæsthetic next falls below the minimum threshold concentration necessary to depress the areas of motor co-ordination of the brain. Muscle tone returns first in the intercostal muscles and the sternocostal part of the diaphragm; breathing loses its jerky character, the tracheal tug disappears, breathing becomes deeper, and expiration is less prolonged. Muscle tone next returns in the upper abdominal muscles, and abdominal contents begin to be pushed into the laparotomy wound, while the breathing becomes deeper, with inspiration and expiration of equal duration, and the pupil grows smaller. It is at this stage that the abdomen is usually closed, and this, together with the returning tone of the lower abdominal muscles, gives further support to the great vessels; as the venous return to the right heart increases, the cardiac output is augmented and the blood pressure rises, while the pulse becomes fuller and slower. Except in the very young, and in subjects suffering from surgical shock, the pupils gradually contract. When at length muscle tone is regained in the lower abdominal muscles, the pupils are small but do not react to light.

The concentration of the inhalation anæsthetic next falls below the minimum threshold concentration necessary to depress the areas of sensory co-ordination of the brain, and the ability to react to external stimulation returns. The reaction to external stimulation is, however, sluggish, and this applies particularly to young

25 years, the present writer has resorted to cardiac massage on two occasions. The first was during a resident anæsthetist appointment (it is quoted in footnote 2 on page 241), and the second was performed for a colleague during the recent war. And it is the writer's experience that an attentive anæsthetist, avoiding chloroform, and when necessary using intravenous fluids, posture and artificial respiration with an oxygen atmosphere, will prevent circulatory collapse during anæsthesia, or will treat it successfully when it does occur.

The recovery of the vital medullary centres from anæsthetic overdose is accompanied by the following clinical signs. The response of the cardiovascular system to the relief of anæsthetic overdose and anoxia is rapid. The pulse, which is at first thin, thready and perhaps irregular, soon becomes fuller and regular, the blood pressure rises; the pink colour of an adequately oxygenated subject returns in the skin and mucous membranes; and the capillary response to pressure returns, although it may be sluggish. If by continued artificial respiration with an oxygen atmosphere the pink colour of adequate oxygenation is maintained, this indicates an effective circulation which will continue to improve as the vital medullary centres progressively recover from the fatigue produced by overdose and anoxia, and as in turn the return of spontaneous breathing increases the venous return to the right heart. There is an overwhelming desire amongst inexperienced anæsthetists to hasten the return of spontaneous breathing, but the imprudent use of carbon dioxide in inspired air is at this juncture, in effect, " whipping a tired horse," and may result in a return of circulatory distress. The frequent removal of the mask to ascertain if spontaneous breathing has returned, interrupts artificial respiration, and the anoxia which it entails may also produce a return of circulatory collapse. Spontaneous breathing cannot return until the tension of the anæsthetic in the respiratory centre is below the minimum threshold concentration necessary to depress it; all that is required is quietly to continue artificial respiration with an oxygen atmosphere and allow the excretion of the inhalation anæsthetic to effect the inevitable ultimate recovery of the respiratory centre. It must be remembered, however, that artificial respiration may produce an acapnœa; if this occurs, the addition

exclusion of gross external stimulation by efficient nursing, both emotional instability and the exaggerated response to external stimulation is effectively neutralized during the non-cooperative stupor stage of anæsthetic recovery. Meanwhile, the excretion of the inhalation anæsthetic proceeds unhindered, and long before the effect of the post-operative morphia has worn off, the concentration of the anæsthetic has fallen below the threshold concentration necessary to depress even the most susceptible type of nervous tissue cell. If then post-anæsthetic medication is adequate and post-anæsthetic nursing is efficient, consciousness is regained and the subject enters the stage of co-operative stupor in a peaceful manner and without incident.

If the subject is not protected in this manner, restlessness during the non-cooperative stupor stage of recovery is the rule rather than the exception after anæsthesia of short duration, and this is more particularly so when the excretion of the inhalation anæsthetic is slow. After an anæsthetic of long duration and/or if the subject is exhausted or shocked, and particularly if this fatigue has been produced by anoxia, restlessness is not common. It is characteristic of the non-cooperative stupor stage of anæsthetic recovery that once restlessness is established, it is difficult or even impossible safely to control it. In an especially violent subject, a dose of 1 grain of morphia may fail to control excitement in this stage of recovery. It is characterised by an excessive and exaggerated response of the body to external stimulation, and muscular activity may be so violent as to require manual restraint. Glands secrete excessively, and Robbins (1935) states that in this period of recovery the secretion of the salivary glands increases 400 per cent. after di-ethyl ether and chloroform anæsthesia, and 350 per cent. after cyclopropane anæsthesia. Coughing, gagging and vomiting are readily produced, and asphyxia may complicate the general restlessness. When restlessness is established in di-ethyl ether anæsthesia, it should not exceed 10-15 minutes, which is approximately the time taken to excrete sufficient di-ethyl ether to reach the stage of co-operative stupor, but a conjoined hysteria may prolong excitement beyond these limits With inhalation anæsthetics, such as nitrous oxide, the duration of restlessness is diminished in keeping with its more rapid excretory rate.

children, and to adults who have been subjected to prolonged anæsthesia or who are shocked. The pupils are small and now react to light, but in small children and in adults suffering from surgical shock, the pupils may remain dilated but react sluggishly to light. Since the lacrimal glands now react to external stimulation, the conjunctiva becomes moist and shiny, and tears may flow. The corneal and conjunctival reflexes return early after short anæsthetics, but after prolonged anæsthesia they remain in abeyance until anæsthetic recovery is almost complete. The salivary and bronchial glands can react, but seldom do. The ability to sweat returns early in this stage of recovery; during tonsillectomy, "sweating" of the palate precedes the return of the cough and gag reflex, and may be the earliest clinical sign of lightening anæsthesia. Soon after the cough and gag reflex becomes active, the swallowing and the vomiting reflexes return. In the absence of stimulation, breathing is regular, shallow and with prolongation of inspiration, while the heart rate slows and the blood pressure tends to return to normal, but external stimulation may produce irregularities of respiratory rhythm and an increase in the pulse rate and pulse pressure.

Recovery from anæsthetic sleep is the danger period of anæsthetic recovery, for on entering the stage of non-cooperative stupor, the subject again becomes hypersensitive to stimulus and emotion is uninhibited. It differs from the non-cooperative stupor stage of induction in two important respects. Firstly, after anæsthesia of any length, the appreciation of external stimuli is dulled, and reflex cardiac inhibitions consequently seldom if ever occur; secondly, it is impossible during this period materially to hasten the excretion of the anæsthetic and so shorten the stage of hypersensitiveness It is, however, possible to by-pass this stage by the injection of morphia as soon as reflex movement appears during the preceding stage of anæsthetic sleep Morphia (in doses of grains 1/6-1/4) diminishes the body's sensibility to lasting impressions such as give rise to pain, etc.; and morphia depresses attention and weakens the subject's appreciation to external stimulation. In consequence of this, while a sudden sharp stimulus may give rise to a normal or even an exaggerated reflex response, attention is not held, and if post-anæsthetic morphia is combined with the

CHAPTER XIII

THE CONTROL OF INHALATION ANÆSTHETICS IN CLINICAL PRACTICE

THE relevant information for the control of the action of inhalation anæsthetics in man has been reviewed, and it is clear that clinical control depends upon a knowledge of the mode of absorption of the particular inhalation anæsthetic combined with a knowledge of the clinical signs of depression of the several areas of functional activity of the brain.

Before discussing the control of particular inhalation anæsthetics in clinical practice, it is first necessary to consider the aims of the anæsthetist. Anæsthesia has been defined as "*The controlled, freely reversible depression of the central nervous system, produced as an aid to surgery by anæsthetic drugs.*" If this definition is accepted, the two major duties of the anæsthetist become obvious. Since the operative words in this definition are "*controlled, freely reversible depression*" and "*as an aid to surgery*," it is clear that the safety of the subject is the primary consideration, and that the only reason for the production of a state of anæsthesia is to make safe surgical interference possible. The aim of the anæsthetist is, therefore, the production of a safe anæsthetic preparation which at the same time must satisfy not only the requirements of the proposed surgical interference, but also the needs of the *particular* surgeon.

If safety is to be the first consideration, anæsthetic depression of the central nervous system must always stop short of depression of the vital medullary centres. It is also essential that the depressing effect of anoxia on the nervous system shall not be added to the selective inhibition of the oxidation of specific carbohydrate metabolites of the nervous system produced by the anæsthetic, for the effect of anoxia is uncontrollable, and it may produce irreversible depression of the cells of the nervous system. Total anoxia for five to eight minutes in an un-anæsthetised subject may be fatal, and, when total anoxia is added to the depressing effects of

During the co-operative stupor stage of recovery, the subject is normal, except for a slow cerebration and amnesia; unless hysteria occurs, he will co-operate in a slow but intelligent manner. Finally, memory returns and anæsthetic recovery is complete.

References.

1. Bailey, Hamilton. (1941). *Brit. med. J.* 19th July. p. 84.
2. Robbins, B H. (1935). *J. Pharmacol.* 54, 426.

the production of anæsthetic depression of the central nervous system to the level of the complete depression of the areas of sensory co-ordination of the brain, in as swift and as trouble-free a manner as is possible. The errors and accidents which occur during inhalation anæsthesia are confined almost entirely to two periods of induction. The first danger period terminates when an effective concentration of the anæsthetic has been fixed by the higher centres of the brain. This results in loss of consciousness Until consciousness is lost, the excessive and exaggerated response to emotional and physical stress which occurs during the period of non-cooperative stupor may produce an overaction of cardiac and other reflexes, designed normally to protect. With loss of consciousness and the complete abolition of psychic factors, however, emotion ceases, and from this time onwards in anæsthesia, irrational response to external stimulation is abolished. The second danger period ends when an effective concentration of the anæsthetic has been fixed in the cells of the areas of sensory co-ordination of the brain The anæsthetic depression of this area of functional activity abolishes the subject's ability to react in a reflex manner to all excepting the most intense proprioceptive stimulation, and from this time onwards in anæsthesia, external stimulation no longer produces excessive reflex response. From the time the areas of sensory co-ordination of the brain have been completely depressed, and until the vital medullary centres are depressed by anæsthetic overdose, the subject is, in effect, a standard biological preparation that reacts only to changes in his internal environment —his blood—and in this instance the subject's reaction to any given set of circumstances during anæsthesia is clear cut and predictible

If the subject is to be protected to the utmost during anæsthesia, it is, therefore, necessary to hasten the absorption of the inhalation anæsthetic and establish an effective concentration of the anæsthetic in the higher centres and the areas of sensory co-ordination of the brain in the shortest possible time, for in this manner, the period during which emotion and/or external stimulation can act in a harmful manner is reduced to the smallest possible duration. Finally, it is essential that the response of the subject shall be the standard sequence of anæsthetic response, already defined.

anæsthetics on the central nervous system, the speed with which the vital medullary centres are irreversibly depressed is correspondingly increased. Moreover, the fatigue produced in the various brain centres by oxygen lack renders the interpretation of the clinical signs of anæsthetic depression of the central nervous system difficult, for, when anoxia is present, it is impossible to decide how much these clinical signs are to be attributed to anoxia on the one hand, and to the anæsthetic agent employed on the other hand In an adequately oxygenated subject, however, the clinical signs of depression of the central nervous system can be attributed solely to the anæsthetic concentrated at the site of narcotic fixation in the cells of the central nervous system. In spite of qualified assertions to the contrary, it is the duty of the anæsthetist to avoid anoxia at all costs. In this discussion, it is assumed throughout that adequate intracellular oxygenation is always present.

Adequate oxygenation can be readily achieved and maintained during clinical anæsthesia if respiratory obstruction is avoided and if the partial pressure of oxygen in inspired air is sufficient for the needs of the particular subject. By trial and error, a position of the head and neck can always be found which permits the subject to breathe in an unobstructed manner, but if difficulty is encountered, one of the many types of airway in common clinical use will aid the anæsthetist to obtain an unobstructed airway. In certain circumstances, an efficient airway can be achieved and maintained only by the passage of an endotracheal catheter, but it must be remembered that even an endotracheal catheter may become kinked or otherwise obstructed.

Adequate oxygenation of the subject is assessed on the colour of the particular subject, and it can be said that his intracellular oxygen demands are satisfied during anæsthesia by the smallest partial pressure of oxygen in the anæsthetic atmosphere that will maintain the subject a bright pink colour throughout. It is important to realize that this represents an adequate volume of oxygen at a *pressure* sufficient to satisfy the intracellular oxygen needs, for *it is the pressure of the gas that determines the direction and the rate of its movement.*

The next duty of the anæsthetist, in the interest of safety, is

been assumed between alveolar air and the anæsthetic atmosphere. Anæsthetic equilibrium is assumed rapidly between alveolar air and the anæsthetic atmosphere in the case of chloroform, cyclopropane and trichlorethylene, whose solubility in whole blood is very small. It is assumed fairly rapidly in the case of nitrous oxide, ethylene and acetylene, for these anæsthetics are more highly soluble in whole blood. *Because of their high solubility in* whole blood, anæsthetic equilibrium between alveolar air and an anæsthetic atmosphere of constant composition containing di-ethyl ether, di-vinyl ether or ethyl chloride, is not achieved until absorption is well advanced. It follows that the use of carbon dioxide in inspired air materially hastens the absorption of di-ethyl ether, di-vinyl ether and ethyl chloride throughout the whole period of anæsthetic induction. It hastens the absorption of nitrous oxide, ethylene and acetylene during the first five minutes of induction; with chloroform, cyclopropane and trichlorethylene, its field of usefulness is even more restricted, and it is seldom necessary nor desirable.

Overpressure is the second means of increasing the rate of absorption and, in turn, the speed of induction with inhalation anæsthetics. Table 36 shows that the standard sequence of response is produced when overpressure is used, with all the inhalation anæsthetics in common clinical use except chloroform, cyclopropane and trichlorethylene. It follows that a swift anæsthetic induction can be safely achieved by the use of overpressure of varying degrees with all the inhalation anæsthetics cited in Table 36, excepting only chloroform, cyclopropane and trichlorethylene. With these three anæsthetics, a graduated method of induction is, in spite of its slowness, imperative if the sequence of response of the body to these three anæsthetics is to be the standard sequence.

These attributes of the inhalation anæsthetics in common clinical use are, together with their anæsthetic potency, shown in Table 36, and permit these nine inhalation anæsthetics to be divided into three broad groups. In clinical anæsthetic practice, the pattern of behaviour of each group, and the methods adopted for the control of the anæsthetics of each group, have much in common.

Reference to Table 36 shows that the members of the first group of inhalation anæsthetics are weak anæsthetics, a fact which

The aim of the anæsthetist in every instance is, therefore, to avoid anoxia throughout, to control absorption in such a manner as to produce the standard sequence of the response of the body to anæsthetics without overdose, and to achieve induction to the level of the complete depression of the areas of sensory co-ordination of the brain in the shortest possible time.

The extent to which this aim can be realized determines the safety and clinical efficiency of particular inhalation anæsthetics and this, in turn, depends upon the physical and the pharmacological properties of the particular anæsthetic; for these properties combine to determine the mode of its absorption by the body, the sequence of the biological response of the body to its action when overpressure is used, and its anæsthetic potency. Together, they determine the field of clinical usefulness of the particular inhalation anæsthetic, and when taken with a knowledge of the signs of anæsthesia, they indicate the method of administration which *should be adopted to control the action of each particular* inhalation anæsthetic in clinical practice.

The control of inhalation anæsthetics in clinical practice is vested in two variables, namely the partial pressure of the anæsthetic in the atmosphere to which the body is exposed, and the volume of effective lung ventilation.

In resting conditions, when the respiratory and circulatory rates are uniform, the body absorbs an inhalation anæsthetic from an anæsthetic atmosphere of constant composition, at a rate which is characteristic of its absorption coefficient, the mass of anæsthetic absorbed by the several areas of functional activity of the brain, and in consequence, the level of anæsthetic depression produced, varies in an upward and a downward direction as the partial pressure of the anæsthetic in the anæsthetic atmosphere. The rate at which this atmosphere achieves anæsthetic equilibrium with alveolar air materially influences the rate at which the several areas of functional activity of the brain attain anæsthetic equilibrium with the anæsthetic atmosphere· deep breathing hastens and shallow breathing retards the speed of anæsthetic induction. The use of carbon dioxide in inspired air during anæsthesia therefore increases the speed of anæsthetic induction, but reaches the limit of its usefulness in this respect when anæsthetic equilibrium has

determines the field of their clinical usefulness and the method of their administration. It is proposed to consider the method of control of each member of this group in terms of the ideal anæsthetic induction discussed above.

TABLE 37.

THE LEVEL OF ANÆSTHETIC DEPRESSION PRODUCED IN MAN AND MAMMALS BY SEVERAL PARTIAL PRESSURES OF NITROUS OXIDE IN THE ABSENCE OF ANOXIA (MODIFIED FROM KOCKMANN, 1936).

Partial pressure Mm. of Hg.	Response	Stage of anæsthesia	Subject
304	Orientation confused	Approaching amnesia	Man
608	Restlessness	Non-cooperative stupor	Man
760	Sleep: Corneal reflex present	Anæsthetic sleep	Man
965	Useful narcosis	Sensory loss	Man & Dog
1320	Incomplete muscular relaxation	Motor loss	Cat
1440	Lateral position Complete muscular relaxation	Motor loss complete	Mouse & Rat
2280	Respiratory paralysis	Complete depression of respiratory centre	Mouse & Rat

Nitrous oxide is a weak anæsthetic gas. It was found by Bert (1878, 1885) in mice, rats and sparrows, by Kemp (1897) in dogs, by Bock (1913) in rats and by Lendle (1928, 1929) in white mice, that in the absence of anoxia a partial pressure of about 2280 mm. of mercury of nitrous oxide was required in the anæsthetic atmosphere to produce death of the experimental animal by paralysis of the respiratory centre. Bert observed, and Kockmann (1936) agrees, that there is a strict parallelism between the action of nitrous oxide in man and mammals. Table 37, modified from Kockmann, represents the partial pressure of nitrous oxide in an anæsthetic atmosphere required to produce the various levels of anæsthetic depression of the brain without oxygen lack

TABLE 36

THE FACTORS RESPONSIBLE FOR THE PATTERN OF BEHAVIOUR OF THE INHALATION ANÆSTHETICS IN COMMON CLINICAL USE.

Anæsthetic	Anæsthetic atmosphere and Alveolar Air assume gaseous equilibrium	Biological Response with Overpressure	Anæsthetic Potency
Nitrous Oxide Ethylene Acetylene	Fairly rapidly	Standard Response	Low—cannot relax abdominal muscles. Low—relaxation of lower abdominal muscles sometimes possible. Low—relaxation of lower abdominal muscles possible.
Ethyl chloride Di-ethyl ether Di-vinyl ether	Slowly	Standard Response	High—can depress the Vital Medullary Centres
Cyclopropane Chloroform Trichlorethylene	Rapidly	Standard Sequence of Response can be distorted	High—can depress the Vital Medullary Centres Low—cannot relax abdominal muscles

pushed to the point of respiratory failure. As such, this procedure must be emphatically condemned.

Ethylene is a more potent anæsthetic than nitrous oxide, and a partial pressure of 600 mm. of mercury of ethylene in the anæsthetic atmosphere will depress the brain to the level of the areas of sensory co-ordination without anoxia. After suitable premedication, loss of muscle tone in the lower abdominal muscles may be produced with this ethylene-oxygen atmosphere in a suitable subject without anoxia; but in clinical practice it is not possible to produce loss of muscle tone in the upper abdominal muscles with ethylene—much less depression of the vital medullary centres—when the subject is adequately oxygenated. It is clear, too, that overpressure cannot be used with ethylene in the conditions which obtain in clinical practice, if anoxia is avoided.

Acetylene is a more potent anæsthetic than ethylene, and anæsthesia to the level of the depression of the areas of sensory co-ordination of the brain can be obtained with a partial pressure of about 530 mm. of mercury in the anæsthetic atmosphere. At a partial pressure of 600 mm. of mercury of acetylene in the anæsthetic atmosphere, loss of muscle tone in the lower abdominal muscles is produced and, after adequate premedication in a subject whose resistance has been diminished, it is sometimes possible to produce relaxation of the upper abdominal muscles; but loss of muscle tone in the intercostal muscles and depression of the vital medullary centres cannot be produced without anoxia, in the conditions which obtain in clinical practice. In an adequately oxygenated subject, acetylene cannot depress the vital medullary centres and overpressure cannot be used with this inhalation anæsthetic, if anoxia is avoided.

In the conditions which obtain in clinical practice, the greatest partial pressure possible in an anæsthetic atmosphere with nitrous oxide, ethylene or acetylene is insufficient to depress the vital medullary centres of an adequately oxygenated subject, and overpressure cannot be used with these three anæsthetics. Therefore —and also because the response of the body to these three inhalation anæsthetics is the standard response—it is impossible to depress the functional activity of non-nervous tissues (*e.g.* the heart) with nitrous oxide, ethylene and acetylene in the conditions

in an un-premedicated subject. It is seen that a partial pressure of 760 mm. of mercury of nitrous oxide is required to produce anæsthetic sleep, and that 2280 mm. of mercury of nitrous oxide is necessary to depress the respiratory centre in an un-premedicated subject if anoxia is avoided.

It can be assumed that the lowest partial pressure of oxygen in an anæsthetic atmosphere compatible with absolute safety from oxygen lack is 160 mm. of mercury; if this figure is accepted, then the greatest partial pressure which any inhalation anæsthetic can exert in an anæsthetic atmosphere at mean sea level, if oxygenation is adequate, is 600 mm. of mercury. This greatest partial pressure, 600 mm. of mercury, is applicable only to an efficient closed system of breathing. In a semi-open system, this figure will be reduced by up to 87 mm. of mercury by the partial pressure of the excreted carbon dioxide and water vapour. In clinical practice, this figure may be increased by 10-15 mm. of mercury by the use of positive pressure. Hence, the partial pressure of nitrous oxide required to depress the vital medullary centres without anoxia, viz. 2280 mm. of mercury, *is more than three times greater than the highest partial pressure of nitrous oxide which it is possible to obtain in the anæsthetic atmosphere in clincal practice without anoxia, viz. 600 mm. of mercury* If premedication is adequate and oxygen lack is avoided, clinical experience shows that a partial pressure of 600 mm. of mercury of nitrous oxide is sufficient in most healthy subjects to produce anæsthesia to the level of the depression of the areas of sensory co-ordination of the brain in Man; in subjects whose resistance has been diminished by surgical shock, disease, etc., a slightly deeper level of anæsthetic depression may occasionally be obtained with this anæsthetic atmosphere. Nitrous oxide is thus a weak anæsthetic, *and in the conditions which obtain in clinical practice, it is quite impossible to depress the vital medullary centres with this anæsthetic if anoxia is avoided* It is clear, too, that overpressure cannot be used with nitrous oxide in the conditions obtaining clinical practice The so-called secondary saturation of McKesson will be recognised as an attempt to use overpressure with nitrous oxide, but since the attempt is made by entirely depleting the anæsthetic atmosphere of oxygen, it is nothing less than simple asphyxiation with nitrous oxide.

solution of about 50 mm. of mercury. Since, at a room temperature of 20°C, the vapour pressure of the least volatile of these three anæsthetics, viz. di-ethyl ether, is about 450 mm. of mercury at mean sea level, it is clear that they can all depress the vital medullary centres of an adequately oxygenated subject in the conditions which exist in clinical practice. They are all potent anæsthetics, and the problem of simple asphyxiation should therefore never arise in clinical practice with these three anæsthetics.

In clinical practice, the greatest partial pressure of di-ethyl ether which it is possible to achieve in inspired air, without the use of special apparatus, is about 136 mm. of mercury or 18 per cent. of the anæsthetic atmosphere at mean sea level. Unless liquid di-ethyl ether at the source of supply is heated during anæsthesia, its temperature and in turn its vapour pressure falls as evaporation proceeds, to reach about 180 mm. of mercury at the source of supply when the temperature of liquid di-ethyl ether has fallen to 0°C. In these conditions, simple asphyxiation is impossible with di-ethyl ether, even when air is used as a source of oxygen supply, if an unobstructed airway is maintained and if the volume of effective lung ventilation is adequate. When, however, liquid di-ethyl ether is heated above its boiling point of 34°C it becomes a gas below its critical temperature, and simple asphyxiation can readily occur. This danger is the main objection to the use of apparatus such as the Oxford Vapouriser No. 2 and the Pinsen Bomb. Simple asphyxiation is unlikely to occur when a di-ethyl ether - air mixture is used at mean sea level with the Oxford Vapouriser No. 1, for this apparatus is designed to maintain di-ethyl ether at a constant temperature of about 28°C, which is equivalent to a constant vapour pressure in the apparatus of about 590 mm. of mercury of di-ethyl ether. When this apparatus is used at altitudes of 7,000 feet and over, *oxygen, and not air*, must be used if the danger of simple asphyxiation is to be avoided.

At room temperature, di-vinyl ether, which at mean sea level boils at 28°C, exerts a vapour pressure of about 560 mm. of mercury, in the conditions which obtain in clinical practice, di-vinyl ether at room temperature is comparable to di-ethyl ether heated to a constant temperature of about 28°C. It is a potent anæsthetic, more volatile than di-ethyl ether, but in clinical practice

which obtain in clinical practice. For these several reasons, *a graduated method of induction with these three inhalation anæsthetics has no point*, and it is clear that no danger will accrue and material protection will be provided, when a swift anæsthetic induction to the level of depression of the areas of sensory co-ordination of the brain is carried out in an adequately oxygenated subject with nitrous oxide, ethylene and acetylene. This can be safely accomplished if rebreathing is employed during induction to hasten the assumption of anæsthetic equilibrium between alveolar air and the anæsthetic atmosphere, and if induction is commenced with the greatest partial pressure of these three anæsthetics possible in the anæsthetic atmosphere without anoxia. Thus, anæsthesia is commenced with an atmosphere of pure nitrous oxide, ethylene or acetylene with partial rebreathing, and oxygen is *immediately* added to this atmosphere at a rate just sufficient to keep pace with the change of colour which would otherwise inevitably occur. In this fashion, the absorption of these anæsthetic gases is as rapid as possible, anæsthetic depression even with the most potent member of the group (acetylene) cannot depress the vital medullary centres, and the smallest partial pressure of oxygen in the anæsthetic atmosphere compatible with efficient oxygenation is determined as rapidly and as accurately as possible. A swift and trouble-free induction is achieved, without anoxia, to the level of depression of the areas of sensory co-ordination of the brain, and the aim of the anæsthetist has been realized.

Because of their relative impotency, the simple asphyxiant action of these three inhalation anæsthetics is the greatest and the only danger to be anticipated in a healthy subject; and if the level of anæsthetic depression required is greater than can be expected of the anæsthetics of this group, then an anæsthetic adjuvant such as di-ethyl ether must be employed, to satisfy the needs of the surgeon without anoxia. Acetylene has been used very infrequently in this country. Ethylene is best used in a closed system of breathing, for it is inflammable and has a penetrating, objectionable odour.

All three anæsthetics of the second group, di-ethyl ether, di-vinyl ether and ethyl chloride, depress the functional activity of the areas of motor co-ordination of the brain at a tension in

atmosphere is increased to about 120 mm. of mercury, *as rapidly as the pharyngeal and laryngeal reflexes permit.* In consequence of these measures, the absorption of di-ethyl ether is rapid, the response of the body to its action is the standard response, and a knowledge of the signs of anæsthesia enables anæsthetic depression to be carried to the level of depression of the areas of sensory co-ordination of the brain, swiftly, without anoxia and with the utmost safety. At this point, as already described, the partial pressure of di-ethyl ether in the anæsthetic atmosphere is reduced to about 50 mm. of mercury, the addition of carbon dioxide to the anæsthetic atmosphere is discontinued, and the level of anæsthetic depression is then adjusted to the requirements of the proposed surgical procedure and the needs of the surgeon. Di-ethyl ether, however, is irritating to the respiratory tract, and as long as the pharynx and larynx retain their ability to react to external stimulus, coughing and gagging may delay the use of adequate overpressure. When adequate premedication is followed by induction with pentothal, nitrous oxide and oxygen, the lower threshold to stimulus and the response to added carbon dioxide combine to permit the early use of overpressure with di-ethyl ether.

atmosphere is increased to about 120 mm. of mercury, *as rapidly as the pharyngeal and laryngeal reflexes permit.* In consequence of these measures, the absorption of di-ethyl ether is rapid, the response of the body to its action is the standard response, and a knowledge of the signs of anæsthesia enables anæsthetic depression to be carried to the level of depression of the areas of sensory co-ordination of the brain, swiftly, without anoxia and with the utmost safety. At this point, as already described, the partial pressure of di-ethyl ether in the anæsthetic atmosphere is reduced to about 50 mm. of mercury, the addition of carbon dioxide to the anæsthetic atmosphere is discontinued, and the level of anæsthetic depression is then adjusted to the requirements of the proposed surgical procedure and the needs of the surgeon. Di-ethyl ether, however, is irritating to the respiratory tract, and as long as the pharynx and larynx retain their ability to react to external stimulus, coughing and gagging may delay the use of adequate overpressure. When adequate premedication is followed by induction with pentothal, nitrous oxide and oxygen, the lower threshold to stimulus and the response to added carbon dioxide combine to permit the early use of overpressure with di-ethyl ether.

Kockmann (1936) asserts that the physical properties of di-vinyl ether are similar to those of di-ethyl ether, and Leake and Chen (1930) estimate that its oil/water partition coefficient is 2 5. If these facts are so, the response of the body to di-vinyl ether should be the standard response when overpressure is used, and clinical experience appears to confirm this premise. Because di-vinyl ether is relatively non-irritating to the respiratory tract, overpressure can be used early in anæsthetic induction; because it is a volatile substance, excessive overpressure can readily be inadvertently used The method of induction with di-vinyl ether is, therefore, similar to that of di-ethyl ether. Rebreathing and overpressure are employed to hasten induction to the level of complete sensory loss, but an outside source of carbon dioxide is seldom necessary. Overpressure should be used with *discrimination and judgment*, for di-vinyl ether is a potent volatile anæsthetic vapour.

The physical properties of ethyl chloride, such as we know them, suggest that ethyl chloride has an oil/water partition coefficient similar to that of nitrous oxide, for the relative solubility

of ethyl chloride in water (2 35 c.c.) to its solubility in whole blood (2 50 c.c.) is of the same order as that of nitrous oxide in these two solvents. Moreover, clinical experience indicates that the response of the body to its action when overpressure is used is the standard response. Anæsthetic equilibrium is assumed between alveolar air and an anæsthetic atmosphere of constant composition containing ethyl chloride, more slowly than is the case with nitrous oxide and more rapidly than has been seen to occur with di-ethyl ether. The use of rebreathing during an ethyl chloride induction is, therefore, a correct and a logical procedure, and it is invariably used in clinical practice. Since ethyl chloride is non-irritating to the respiratory tract, and because it is a gas below its critical temperature in the conditions which obtain in clinical practice, overpressure may be used early in induction with this anæsthetic. The problem with ethyl chloride, however, is to use sufficient overpressure to depress the brain swiftly to the level of complete sensory loss, without at the same time inadvertently depressing the vital medullary centres, for it is a potent and very volatile anæsthetic. Ethyl chloride, therefore, follows the pattern of behaviour of the two ethers, and with this anæsthetic, rebreathing and overpressure should be used to hasten anæsthetic induction to the level of complete sensory loss. *The imprudent use of overpressure may readily lead to overdose with secondary cardiac failure*, which is the cause of most deaths during ethyl chloride anæsthesia, and with this anæsthetic, overpressure must be used with care and discrimination.

It is clear that a knowledge of the signs of anæsthesia, coupled with a knowledge of the pattern of behaviour of these three anæsthetics, permits a swift induction to the level of depression of the areas of sensory co-ordination of the brain without anoxia. Overpressure may be freely used with di-ethyl ether, but with the other two relatively non-irritating and less soluble members of this group, the imprudent use of overpressure may produce depression of the vital medullary centres. The danger increases as their volatility and potency, to be greatest for ethyl chloride. The field of clinical usefulness of the two ethers is broader than the inhalation anæsthetics of the first group: alone or in combination with the members of the first group, they may be employed to

produce full muscular relaxation in clinical practice. Ethyl chloride is not suitable for the production of deep prolonged anæsthesia; and in a series of 45 cases in which deep ethyl chloride anæsthesia was maintained for more than 30 minutes cerebral convulsions occurred in 20 per cent. of these cases.[1] On this account, ethyl chloride is employed for anæsthetic induction and/or for minor surgical procedures of short duration.

The third group of inhalation anæsthetics consists of cyclopropane, chloroform and trichlorethylene. Cyclopropane is a gas above its critical temperature, and chloroform and trichlorethylene are vapours which exert a vapour pressure, at 20°C, of about 160 mm. of mercury and 60 mm. of mercury respectively. These three drugs are potent narcotics and are sparingly soluble in whole blood. Cyclopropane and chloroform are potent anæsthetics, capable of depressing the vital medullary centres of an adequately oxygenated subject. Because of its low vapour pressure and its poor solubility in whole blood, trichlorethylene, which is a potent narcotic, is a relatively weak anæsthetic; in the conditions which obtain in clinical practice, it is impossible with this anæsthetic to produce either loss of muscle tone in large muscle groups, or depression of the vital medullary centres in a healthy adult.

Because of their high oil/water partition coefficient, these three anæsthetics are absorbed by the heart more rapidly than by the brain, and a distortion of the standard sequence of response may be produced when overpressure is used with them. This takes the form of cardiac arrythmias, which may be quickly followed by primary cardiac failure unless the partial pressure of these anæsthetics in the anæsthetic atmosphere is immediately reduced. *It follows that overpressure must never, and a graduated method of induction must always, be used with these three inhalation anæsthetics*

It is not a simple matter to administer a graduated induction with these three anæsthetics for the following reasons. Because they are sparingly soluble in whole blood, anæsthetic equilibrium is rapidly assumed between alveolar air and an anæsthetic atmosphere containing any of this third group, and from this time

[1] In this series of cases, ethyl chloride was used in a closed system of breathing, either with oxygen or as an adjuvant to nitrous oxide and oxygen anoxia was avoided throughout.

of ethyl chloride in water (2·35 c.c.) to its solubility in whole blood (2·50 c.c.) is of the same order as that of nitrous oxide in these two solvents. Moreover, clinical experience indicates that the response of the body to its action when overpressure is used is the standard response. Anæsthetic equilibrium is assumed between alveolar air and an anæsthetic atmosphere of constant composition containing ethyl chloride, more slowly than is the case with nitrous oxide and more rapidly than has been seen to occur with di-ethyl ether. The use of rebreathing during an ethyl chloride induction is, therefore, a correct and a logical procedure, and it is invariably used in clinical practice. Since ethyl chloride is non-irritating to the respiratory tract, and because it is a gas below its critical temperature in the conditions which obtain in clinical practice, overpressure may be used early in induction with this anæsthetic. The problem with ethyl chloride, however, is to use sufficient overpressure to depress the brain swiftly to the level of complete sensory loss, without at the same time inadvertently depressing the vital medullary centres, for it is a potent and very volatile anæsthetic. Ethyl chloride, therefore, follows the pattern of behaviour of the two ethers, and with this anæsthetic, rebreathing and overpressure should be used to hasten anæsthetic induction to the level of complete sensory loss. *The imprudent use of overpressure may readily lead to overdose with secondary cardiac failure*, which is the cause of most deaths during ethyl chloride anæsthesia, and with this anæsthetic, overpressure must be used with care and discrimination.

It is clear that a knowledge of the signs of anæsthesia, coupled with a knowledge of the pattern of behaviour of these three anæsthetics, permits a swift induction to the level of depression of the areas of sensory co-ordination of the brain without anoxia. Overpressure may be freely used with di-ethyl ether, but with the other two relatively non-irritating and less soluble members of this group, the imprudent use of overpressure may produce depression of the vital medullary centres. The danger increases as their volatility and potency, to be greatest for ethyl chloride. The field of clinical usefulness of the two ethers is broader than the inhalation anæsthetics of the first group: alone or in combination with the members of the first group, they may be employed to

thetic potency. The pattern of its pharmacological behaviour in Man resembles that of cyclopropane rather than that of chloroform, and it has been in common clinical use in this country for the past eight years. Current clinical reports of its ability and disability during this period repeat on a minor scale the controversy which in the past raged round chloroform. Thus, Ostlere (1948) reported 40,000 trichlorethylene anæsthetics without a death which could be attributed to this anæsthetic; Reynolds (1949) reported 1,168 obstetric cases with trichlorethylene with one death; Struan-Marshall (1947) reported the use of this anæsthetic for 37 cæsarian sections without a maternal death, and Stern (1947) had five maternal deaths in 82 cases during trichlorethylene anæsthesia for the same surgical procedure: R. de Soldenhoff (1949) states that he has knowledge of four deaths during trichlorethylene anæsthesia during the past 12 months, and Helliwell (1948) is of the opinion that trichlorethylene anæsthesia is not without danger. When these figures are considered with the observations of Barnes and Ives (1944), Condon (1948), Haworth and Duff (1943) and others, it is clear that trichlorethylene can be used in clinical practice in a dangerous manner, and there is little doubt that anæsthetists are exercised in their mind, with good reason, about its clinical safety.

The low volatility of trichlorethylene makes it unsuitable for use on an open mask, and it cannot be used in a closed system of breathing, for Carden (1944) and Humphrey and McClelland (1944) have shown that trichlorethylene reacts with soda lime to produce dichloracetylene, which is a noxious substance. It is used in one of the many modifications of the Woolf's bottle in which air, oxygen or nitrous oxide and oxygen, wholly or in part, can be drawn over or passed through the trichlorethylene contained in the bottle. The Boyle's machine or the Marrett's apparatus are commonly used for its administration in clinical anæsthetic practice. With these machines the graduated method of administration, essential for its safe use, can be successfully applied. Since anæsthetic equilibrium is rapidly assumed between alveolar air and a trichlorethylene atmosphere, the use of carbon dioxide from an outside source is unnecessary, and rebreathing serves little useful purpose.

onwards in anæsthetics the smallest alteration in the pa pressure of these anæsthetics in the anæsthetic atmosphere immediately reflected in the anæsthetic content of blood lea the pulmonary capillaries, and, in turn, in the anæsthetic con of tissue cells, such as those of the heart and brain which abs these inhalation anæsthetics rapidly. Hence very small alterati of the partial pressure of these anæsthetics in the anæsth atmosphere are therefore decisive, and overpressure may rea be inadvertently used in clinical practice with dangerous or e fatal results, because of the rapidity of their absorption by heart.

If the response of the subject in this third group of inhalat anæsthetics is to conform to the standard safe sequence response, a graduated method of induction must be employed clinical practice. The dangers introduced by a slow method induction are trivial when compared with the effect of overpressu and the most significant indication of the subject's well-being w these members of the third group is the state of the cardiovascu system during anæsthesia.

For reasons already given in this discussion, the writer consid that it is not a justifiable procedure to administer chloroform clinical practice unless it is found impossible to produce an effici anæsthetic preparation by the substitution of other anæsthe agents. Nowadays, one cannot readily imagine circumstan when this substitution would not be possible, and it is illogic therefore, to describe here in detail the control of chloroform clinical anæsthetic practice. Faultless descriptions of the cont of chloroform can be obtained in the textbooks of the last t decades. It is sufficient to emphasise that atropine should alwa be used as a pre-anæsthetic medicant before chloroform anæsthes that a graduated method of induction should always be employ with this drug, and that the control of its partial pressure inspired air is enhanced if it is administered in an anæsthe apparatus, such as a Boyles machine, rather than with a dr bottle and open mask.

The clinical value of trichlorethylene is still *sub judice*. It a potent narcotic chlor-hydrocarbon resembling chloroform in i chemical and physical properties, but lacking chloroform's anæ

thetic potency. The pattern of its pharmacological behaviour in Man resembles that of cyclopropane rather than that of chloroform, and it has been in common clinical use in this country for the past eight years. Current clinical reports of its ability and disability during this period repeat on a minor scale the controversy which in the past raged round chloroform. Thus, Ostlere (1948) reported 40,000 trichlorethylene anæsthetics without a death which could be attributed to this anæsthetic; Reynolds (1949) reported 1,168 obstetric cases with trichlorethylene with one death; Struan-Marshall (1947) reported the use of this anæsthetic for 37 cæsarian sections without a maternal death, and Stern (1947) had five maternal deaths in 82 cases during trichlorethylene anæsthesia for the same surgical procedure: R. de Soldenhoff (1949) states that he has knowledge of four deaths during trichlorethylene anæsthesia during the past 12 months, and Helliwell (1948) is of the opinion that trichlorethylene anæsthesia is not without danger. When these figures are considered with the observations of Barnes and Ives (1944), Condon (1948), Haworth and Duff (1943) and others, it is clear that trichlorethylene can be used in clinical practice in a dangerous manner, and there is little doubt that anæsthetists are exercised in their mind, with good reason, about its clinical safety

The low volatility of trichlorethylene makes it unsuitable for use on an open mask, and it cannot be used in a closed system of breathing, for Carden (1944) and Humphrey and McClelland (1944) have shown that trichlorethylene reacts with soda lime to produce dichloracetylene, which is a noxious substance. It is used in one of the many modifications of the Woolf's bottle in which air, oxygen or nitrous oxide and oxygen, wholly or in part, can be drawn over or passed through the trichlorethylene contained in the bottle. The Boyle's machine or the Marrett's apparatus are commonly used for its administration in clinical anæsthetic practice. With these machines the graduated method of administration, essential for its safe use, can be successfully applied. Since anæsthetic equilibrium is rapidly assumed between alveolar air and a trichlorethylene atmosphere, the use of carbon dioxide from an outside source is unnecessary, and rebreathing serves little useful purpose.

onwards in anæsthetics the smallest alteration in the partial pressure of these anæsthetics in the anæsthetic atmosphere is immediately reflected in the anæsthetic content of blood leaving the pulmonary capillaries, and, in turn, in the anæsthetic content of tissue cells, such as those of the heart and brain which absorb these inhalation anæsthetics rapidly. Hence very small alterations of the partial pressure of these anæsthetics in the anæsthetic atmosphere are therefore decisive, and overpressure may readily be inadvertently used in clinical practice with dangerous or even fatal results, because of the rapidity of their absorption by the heart.

If the response of the subject in this third group of inhalation anæsthetics is to conform to the standard safe sequence of response, a graduated method of induction must be employed in clinical practice. The dangers introduced by a slow method of induction are trivial when compared with the effect of overpressure, and the most significant indication of the subject's well-being with these members of the third group is the state of the cardiovascular system during anæsthesia.

For reasons already given in this discussion, the writer considers that it is not a justifiable procedure to administer chloroform in clinical practice unless it is found impossible to produce an efficient anæsthetic preparation by the substitution of other anæsthetic agents. Nowadays, one cannot readily imagine circumstances when this substitution would not be possible, and it is illogical, therefore, to describe here in detail the control of chloroform in clinical anæsthetic practice. Faultless descriptions of the control of chloroform can be obtained in the textbooks of the last two decades. It is sufficient to emphasise that atropine should always be used as a pre-anæsthetic medicant before chloroform anæsthesia, that a graduated method of induction should always be employed with this drug, and that the control of its partial pressure in inspired air is enhanced if it is administered in an anæsthetic apparatus, such as a Boyles machine, rather than with a drop bottle and open mask.

The clinical value of trichlorethylene is still *sub judice* It is a potent narcotic chlor-hydrocarbon resembling chloroform in its chemical and physical properties, but lacking chloroform's anæs-

irregularities were excluded. The evidence discussed indicates that this is sound practice, and it can be concluded that trichlorethylene is contra-indicated when pathological conditions of the heart are present or are suspected.

Cyclopropane, which is a gas at room temperature with an oil/water partition coefficient of 43, is the most flexible and controllable of the inhalation anæsthetics with a high oil/water partition coefficient. It is used in a closed system of breathing, for it is inflammable, has a penetrating odour—and is very expensive. Because of the sequence of its absorption, a graduated method of administration must be used with cyclopropane if it is to be used safely, and the use of carbon dioxide from an outside source of supply is unnecessary, for cyclopropane is very insoluble in whole blood. In a healthy subject, the junctional tissue of the heart is not depressed with cyclopropane anæsthesia to the level of complete sensory loss; therefore, the experienced anæsthetist can in the interest of a rapid induction use overpressure to this level with safety. The usual technique of the administration of cyclopropane is as follows. The subject, premedicated with scopolamine and omnopon, is given an appropriate intravenous injection of pentothal. The reservoir of the closed system of breathing is filled with oxygen, its carbon dioxide absorber is by-passed and the facepiece is accurately applied to the subject. The oxygen flowmeter is then adjusted to 300-500 c c. per minute, and cyclopropane is added at the rate of about 300 c.c. per minute. As soon as the movements of the anæsthetic reservoir indicate regular automic breathing, the carbon dioxide absorber is thrown into circuit. In a two-phase system of breathing, the absorption of the carbon dioxide content of the anæsthetic reservoir is effected with 2-3 expirations, and the oxygen intake is now adjusted so that the total pressure in the closed system remains constant at the end of expiration. This manœuvre has the effect of rapidly regulating the oxygen intake to the metabolic rate of the particular subject. In these conditions, at a cyclopropane intake of 300 c.c. per minute, anæsthesia to the level of complete sensory loss is produced in a normal subject of about 70 kilos in 3·5 minutes, but once the oxygen intake has been adjusted to the metabolic rate of the particular subject, the intake of cyclopropane can be cautiously

The physical properties of trichlorethylene such as we know them, and the similarity of its clinical behaviour to cyclopropane, combine to indicate that trichlorethylene reaches anæsthetic equilibrium with the junctional tissue of the heart soon after anæsthesia to the level of complete sensory loss has been achieved. This probability is strengthened when it is observed that trichlorethylene anæsthesia, pushed beyond the level of complete sensory loss, invariably results in rapid breathing, followed by cardiac arrythmias. These cardiac arrythmias have been reported by many observers, and this sequence of events has been observed by all anæsthetists who attempt to produce muscular relaxation with trichlorethylene. Hewer (1946) states that muscular relaxation is sometimes difficult to obtain with trichlorethylene, and that too little is known of the deeper planes of trichlorethylene anæsthesia to warrant the pushing of the drug; but a more pertinent reason for not exceeding the level of complete sensory loss with trichlorethylene would appear to be the fact that cardiac arrythmias follow such attempts even in healthy subjects. If such attempts to produce muscular relaxation are persisted in, these cardiac arrythmias may give place to primary cardiac failure, and it is probable that this was the sequence of events in Stern's cases. For these several reasons, it seems clear that one should not attempt to produce anæsthesia deeper than complete sensory loss with trichlorethylene, and that this limitation of the field of its clinical usefulness must be accepted if it is to be safely used in clinical anæsthetic practice for healthy subjects Superficially, this may seem an easy condition to fulfil, but clinical experience has shown that it is not so, for, when full saturation at the partial pressure of trichlorethylene necessary to produce complete sensory loss is approached, very small alterations in its partial pressure in the anæsthetic atmosphere produce intense and significant results. Evidence has been discussed which indicates that in subjects whose cardiac reserve is impaired, the junctional tissue of the heart is more susceptible than normal to the action of trichlorethylene. In these subjects, cardiac arrythmias may occur when the partial pressure of trichlorethylene in the anæsthetic atmosphere is less than that required to produce anæsthesia to the level of complete sensory loss In Ostlere's series of cases, subjects with cardiac

with consequent lightening of anæsthesia. When at length the body taken as a whole is fully saturated at the tension necessary to produce complete sensory loss, the intake of cyclopropane into the closed system must be arrested, and it will be realized that, as absorption proceeds and non-nervous tissues approach full saturation at this tension, overpressure may the more readily be inadvertently used. Many anæsthetists believe that cyclopropane anæsthesia should not be pushed beyond the level of complete sensory loss, and this conclusion without doubt makes for greatest safety with this anæsthetic. In suitable subjects, however, the experienced anæsthetist may produce loss of muscle tone in trunk muscles without bradycardia and/or cardiac arrythmias if overpressure is avoided. It has been reported that cardiac arrythmias can be arrested by overpressure. The author believes that this is a dangerous practice, and the whole trend of this discussion indicates, moreover, that it has no factual foundation.

It can be concluded that the potent and non-irritating anæsthetic gas, cyclopropane, is a valuable addition to clinical anæsthetic practice. When used in subjects whose cardiac reserve is within normal limits, the character of its uptake permits a swift and trouble-free induction to the level of complete sensory loss; its safety is determined by the method of its administration and a correct assessment of its suitability for the particular subject. If overpressure is employed in a healthy subject beyond the level of complete sensory loss—and this may readily occur because of its potency and its low solubility in blood—a distorted sequence of response may occur, and this takes the form of cardiac irregularities which may terminate in primary cardiac failure. It is for this reason that many anæsthetists never wittingly push cyclopropane anæsthesia beyond the level of complete sensory loss. If cyclopropane is used in subjects whose cardiac reserve is impaired, it is a dangerous anæsthetic, for cardiac irregularities and/or primary cardiac failure may occur in these subjects during light cyclopropane anæsthesia. Perhaps the most significant evidence supporting these conclusions is that of Rink, Helliwell and Hutton (1949). In discussing anæsthesia for the relief of congenital pulmonary stenosis, they consider that cyclopropane to the level of complete sensory loss provides the most satisfactory anæsthetic preparation

varied in an upward or a downward direction in keeping with the needs of the particular subject.

Anæsthetic induction with cyclopropane is swift and, as a rule, trouble-free, and the signs of the level of anæsthetic depression of the subject with this anæsthetic are difficult to assess; a recapitulation of the signs of cyclopropane anæsthesia at the level of complete sensory loss is therefore made here. At this level of anæsthetic depression, breathing is regular and shallow with inspiration and expiration of equal length. Appropriate stimuli produce neither vocalization nor alteration in respiratory rhythm; and lacrimal, salivary and bronchial glands cease to secrete; the eyeball is fixed in the central position and the pupils, which are small, do not react to bright light; reflexes are inactive and skeletal muscles flaccid, but the large muscle groups of the trunk become rigid when appropriate stimulation is applied to them. In healthy subjects, the blood pressure is within normal limits, but the pulse, which may be slightly raised in pressure, is regular and beats at between 70 and 100 per minute. At a cyclopropane intake of 300 c.c. per minute, it may be impossible to reach this level of depression of the brain in a resistant subject. The intake of cyclopropane is then cautiously increased until the signs of complete sensory loss are present, provided only that this does not result in bradycardia below 70 beats per minute and/or irregularity of the rhythm of the pulse. If, however, bradycardia and/or cardiac irregularities do occur, the subject must be considered unsuitable for cyclopropane, and an immediate switch is made to an anæsthetic of the second group.

When cyclopropane anæsthesia at the level of complete sensory loss has been attained, without bradycardia and/or cardiac arrythmias, the intake of cyclopropane is cautiously reduced to the smallest intake which will maintain the subject at this level of anæsthetic depression. It will be necessary to add an ever decreasing amount of cyclopropane to the closed system until anæsthetic equilibrium has been attained between the anæsthetic atmosphere and the tissues, nervous and non-nervous, of the whole body; for until non-nervous tissues are fully saturated the arrest of the intake of cyclopropane into the closed system must result in the deviation of cyclopropane from the brain to non-nervous tissues,

an adequately oxygenated subject in the conditions which obtain in clinical anæsthetic practice. It follows that the field of clinical usefulness of nitrous oxide and ethylene is a limited one and that, in a normal subject, anoxia is the only danger to be anticipated with these two anæsthetics of the first group. The anæsthetics of the second group consist of di-ethyl ether, di-vinyl ether and ethyl chloride, which are sufficiently potent to depress the vital medullary centres of an adequately oxygenated, healthy subject in the conditions which obtain in clinical anæsthetic practice. Because prolonged deep anæsthesia with ethyl chloride is apt to produce cerebral convulsions, the field of its clinical usefulness is limited, and it is employed only for minor surgical procedures and for anæsthetic induction. The two ethers, however, singly or in combination with the members of the first group, are flexible anæsthetics, and can satisfy the anæsthetic requirements for any given surgical procedure. The only danger to be anticipated with these two ethers is anæsthetic overdose; because the standard sequence of anæsthetic response always obtains with these two ethers, overpressure is invariably used in the interest of a rapid induction, and overdose takes the form of secondary cardiac failure. Hence, warning of impending overdose is clear and definite, and these two ethers are the safest and the most flexible inhalation anæsthetics in common clinical use. The third group of inhalation anæsthetics consists of chloroform, cyclopropane and trichlorethylene. They all have a high oil/water partition coefficient, and evidence has been discussed which indicates that their sequence of absorption by the body makes it impossible to avoid primary cardiac failure with these *inhalation anæsthetics when overpressure is imprudently* used. Moreover, overpressure can readily be inadvertently used in clinical practice with these three anæsthetics, for their low solubility in blood ensures that a small increase of their partial pressure in the anæsthetic atmosphere rapidly produces a corresponding increase in their concentration in circulating blood. Chloroform is considered unsuitable for use in clinical anæsthetic practice, for the rapid uptake of chloroform by the junctional tissue of the heart during the stage of non-cooperative stupor renders this tissue susceptible to excess of adrenaline, and adrenaline excess is likely to be greater at this stage of anæsthesia than at any other time

in young subjects with this condition. On clinical grounds they are of the opinion that di-ethyl ether should be used in older subjects with congenital pulmonary stenosis, particularly those who have already shown evidence of cardiac failure, and in cases of post-rheumatic mitral stenosis: for relative anoxia of long duration on the one hand, and on the other, rheumatic disease, have probably produced pathological conditions of the junctional tissue of the heart, which renders cyclopropane a dangerous anæsthetic agent in these subjects.

This discussion indicates that the clinical control of the inhalation anæsthetics in common clinical use depends primarily upon an accurate knowledge of the signs of the anæsthetic depression of the brain, coupled with the accurate minute-to-minute control of the partial pressure of the inhalation anæsthetic in the atmosphere breathed and, in turn, its concentration in circulating blood. The blood concentration of the inhalation anæsthetic, however, must be regulated in such a manner that the standard sequence of anæsthetic response—short of depression of the vital medullary centres —is always produced, and it has been concluded that anæsthesia to the level of complete sensory loss should be attained as rapidly as possible if the subject is to be afforded the greatest possible measure of protection during clinical anæsthesia. The fulfilment of these conditions in clinical anæsthetic practice depends upon the physical properties of the particular inhalation anæsthetic, for a swift induction is possible only when overpressure is used, and the standard sequence of anæsthetic response can be obtained with overpressure only with the inhalation anæsthetics whose oil/water partition coefficient is greater than unity and less than 14. The inhalation anæsthetics whose oil/water partition coefficient falls within these physical limits are the safest anæsthetics in common clinical use, and they may be divided, according to their anæsthetic potency, into two groups. The first group consists of nitrous oxide, ethylene and acetylene, which are sufficiently potent to depress the areas of sensory co-ordination of the brain; a swift induction to this level can be achieved in clinical practice with these anæsthetics. Only nitrous oxide and ethylene are in common clinical use, and they are unable either to depress muscle tone or to depress the vital medullary centres of

9. HELLIWELL, P. J. (1948). *Brit. med. J.* ii, 156.
10. HEWER, C. L. (1946). "Recent Advances in Anæsthesia and Analgesia." 5th Ed. p. 103. J. & A. Churchill Ltd., London.
11. HUMPHREY, J. H., and MCCLELLAND, M. (1944). *Brit. med. J.* i, 316.
12. KEMP, G. T. (1897). *Brit. med. J.* ii, 1480.
13. KOCKMAN, M. (1936). "Handbuch der Experimentellen Pharmakologie Zweiter band." p. 73. Julius Springer, Berlin.
14. LEAKE, C. D., and CHEN, M. Y. (1930). *Proc. Soc. exp. Biol. N.Y.* 28, 151.
15. LENDLE, L. (1928). *Arch exp. Path. Pharmakol.* 138, 152.
Arch exp. Path. Pharmakol. 139, 201.
16. OSTLERE, G. (1948) *Brit. med. J* i, 195.
17. REYNOLDS, F. N. (1949) *Brit. med. J.* i, 537.
18. RINK, E. H., HELLIWELL, P. J., and HUTTON, A. M. (1948). Guy's Hosp. Rep. 97, 48.
19. STERN, D. M. (1947). *Brit. med. J.* i, 199.
20. STRUAN-MARSHALL, J. (1947). *Brit. med. J.* i, 355.

during anæsthetic induction or maintenance. Evidence has been discussed which indicates that the junctional tissue of the heart reaches anæsthetic equilibrium with a cyclopropane or trichlorethylene atmosphere soon after the areas of sensory co-ordination of the brain have become saturated to the partial pressure of cyclopropane or trichlorethylene in the anæsthetic atmosphere; anæsthesia to the level of complete sensory loss can therefore be safely produced with these anæsthetics in healthy subjects. Since the introduction of d-tubo-curarine chloride, this is the greatest level of anæsthetic depression desired or required in clinical anæsthetic practice. Attempts to exceed this level of depression in healthy subjects with cyclopropane are likely to be followed by cardiac arrythmias: with trichlorethylene, cardiac arrythmias will invariably be produced. In subjects whose cardiac reserve is impaired, cardiac arrythmias may occur with cyclopropane and with trichlorethylene during anæsthesia lighter than complete sensory loss. It can be concluded that a graduated method of induction must be employed with cyclopropane and trichlorethylene, that it is unwise with these anæsthetics to produce anæsthesia deeper than complete sensory loss in healthy subjects, and that they are unsuitable for use in subjects whose cardiac reserve is impaired.

This discussion shows that the blood concentration of a volatile anæsthetic—and all that this has been seen to imply—can be controlled in an upward and a downward direction. This is in contrast to the control of the blood concentration of non-volatile anæsthetics which are to be discussed next, for it will be seen that while the uptake of a non-volatile anæsthetic can be regulated accurately, *the rate of its excretion cannot be increased* wittingly and it may be retarded. On this account alone, inhalation anæsthetics must be considered the safest and most flexible anæsthetics in clinical use.

References

1 Barnes, C G, and Ives, J. (1944). *Proc R Soc. Med.* 37, 528
2. Bert, P (1885). *C. R Soc Biol. Paris* 3, 11, 520
3. Bock, J (1913) *Arch. exp. Path. Pharmak* 75, 43
4. Carden, S. (1944). *Brit. med J* i, 319.
5 Condon, H A. (1948) *Brit. med. J* ii, 340.
6 de Soldenhoff, R (1949) *Brit med. J.* i, 634
7. Harris, T A B (1933) Unpublished.
8. Haworth, J, and Duff, A. (1943). *Brit. Med. J.* ii, 381.

since a blood-borne anæsthetic must possess a certain solubility in water to be effective, it follows that solubility must play a part in the uptake of non-volatile narcotics suitable for use as anæsthetics in a heterogeneous cell system.

In Table 38, which is modified from the works of Tabern and Shelburg (1933), the clinical effectiveness of various barbiturates

TABLE 38.

THE FACTORS WHICH INFLUENCE THE CLINICAL EFFECTIVENESS OF SEVERAL BARBITURATES (AFTER TABERN AND SHELBURG, 1933).

Barbiturate	Oil/water partition coefficient	Percentage Adsorption	Surface tension decrease	Clinical effectiveness
Barbitone	0 214	88	99 1	+
Ipral	0 73	—	98·5	+
Dial	0 85	92 5	97·5	+ +
Neonal	2 58	96	89 5	+ + +
Amytal	2·895	95	76· 5	+ + +
Pernocton	4 3	—	91·5	+ + + +
Nembutal	4 4	96	85·5	+ + + +
Pentothal	4·7 (circa)	—	—	+ + + + +

in common clinical use is compared with the intensity of these several factors responsible for their uptake by living cells. It is seen that clinical effectiveness is most closely paralleled by the oil/water partition coefficient of these several barbiturates; this in turn suggests the importance of the water solubility and the lipoid solubility of the particular barbiturate in the mechanism of its absorption to the site of their drug fixation in the cells of a heterogeneous cell system such as Man.

Although little is known of the absorptive capacity of the individual organs of the body for non-volatile anæsthetics, the response of the body to the intravenous injection of a single effective dose of a non-volatile anæsthetic such as evipan or pentothal indicates that an effective concentration is achieved very rapidly in the brain, for anæsthesia occurs within 30-60 seconds, and

CHAPTER XIV

NON-VOLATILE ANAESTHETICS

INTRODUCTION

NON-VOLATILE anæsthetics are liquids and soluble solids at body temperature. Because of their physical state, non-volatile anæsthetics cannot be absorbed into circulating blood through the medium of the respiratory system, and alternative methods of approach suitable to their physical state must be employed to dissolve these anæsthetic liquids and solids in circulating blood in a controllable manner. In clinical practice they are injected intravenously, or they are absorbed into circulating blood from a subcutaneous or an intramuscular site, or from the capillary bed of a hollow viscus.

Once dissolved in circulating blood, non-volatile anæsthetics are disposed of in a manner similar to that of volatile anæsthetics. At each round or passage of the whole volume of blood through the circulatory system, a proportion of its contained non-volatile anæsthetic is carried to the brain, a proportion is carried to other nervous and non-nervous tissues, a proportion is excreted from the body and, finally, a proportion remains in circulating blood to be passed on *via* the venous circulation to the right heart.

The uptake of non-volatile anæsthetics by tissue cells from extracellular fluid is governed by the same factors applying to volatile anæsthetics. Uptake consists essentially in the assumption of equilibrium in respect to the narcotic, between extracellular fluid and the cell itself, solubility, surface tension, adsorption, etc., influence the escape tendency of non-volatile anæsthetics from extracellular fluid to tissue cells These same factors also determine the mass of a particular non-volatile anæsthetic that must be absorbed by a particular type of cell from extracellular fluid to produce this state of equilibrium in the drug-cell system And it is to be expected that the less volatile the narcotic, the greater will be the influence of surface tension and adsorption on uptake; but,

of non-volatile anæsthetics having an oil/water partition coefficient greater than unity and less than about 6, is the standard response, and overdose produces death from secondary cardiac failure. Respiratory depression during evipan or pentothal anæsthesia is often attributed to an individual susceptibility of the respiratory centre to these anæsthetics, but there is no evidence of this, and respiratory failure is always due to anæsthetic overdose. Since the biological response of the body to non-volatile anæsthetics, such as evipan and pentothal, is in general identical with that of volatile anæsthetics of comparable oil/water partition coefficient, it can be assumed that the same factors are acting to produce this result. Blood supply and individual susceptibility may be the only relevant factors, but it is probable that the absorptive capacity of the several areas of functional activity of the brain plays the same decisive rôle that has been seen in the case of volatile anæsthetics. The probability is strengthened when the effect of overdose with barbitone is compared with the use of overpressure with ethyl alcohol or acetone, whose oil/water partition is less than unity. Barbitone has an oil/water partition coefficient of 0 214, and that of ethyl alcohol and acetone is 0 046 and 0·235 respectively. In each instance the vital medullary centres are depressed soon after consciousness is lost, and it is probable, in each instance, that the absorptive capacity of the vital medullary centres is less than that of the higher centres, the areas of sensory and motor co-ordination of the brain as shown in Table 31.

The striking differences observed in the rate of the body's response to an effective dose of various non-volatile anæsthetics, injected intravenously, indicate that the rate of uptake and/or fixation of individual non-volatile anæsthetics varies considerably. Das (1940) observed in mice that the intravenous injection of a medium hypnotic dose of evipan or pentothal produced hypnosis in from 1-2 minutes, and that the intravenous injection of a medium lethal dose of these anæsthetics produced death of the subject in a few minutes. It can be concluded that the uptake of evipan and pentothal by the brain from circulating blood and their subsequent fixation by brain cells are very rapid. The response of the body to avertin and paraldehyde is of the same

maximum anæsthetic depression of the brain is produced within 1-2 minutes of their intravenous injection. These are indications that a state of anæsthetic equilibrium has been produced between brain and blood within 1-2 minutes of the solution of the anæsthetic in circulating blood. Weese's (1937) results show that the blood concentration of evipan in rabbits falls to a level which corresponds to uniform distribution throughout the whole body in about 30 minutes after its intravenous injection, and these facts indicate that the brain absorbs evipan more rapidly than any other organ of the body. Moreover, cardiac arrythmias do not occur in clinical practice with evipan or pentothal, even when anæsthetic overdose has been produced, and it can be concluded that the rate of absorption of evipan and pentothal by the brain is, in fact, more rapid than that of the heart or any other organ of the body. This result might have been anticipated when one recalls that these two non-volatile anæsthetics have an oil/water partition coefficient of about 4 5, for the same sequence of absorption has been seen to obtain with volatile anæsthetics whose oil/water partition coefficient lies between 2 and 4.

Little has been determined experimentally about the sequence of absorption of non-volatile anæsthetics by the different areas of functional activity of the brain, but when the injection of an effective mass of a non-volatile anæsthetic such as evipan, pentothal or avertin into circulating blood is slow enough, the response of the body to their action is the standard response. Consciousness is lost first, in the same way as during inhalation anæsthesia; then the ability to react in a reflex manner to external stimulation is abolished; then motor tone, and finally, if the mass injected is excessive, the vital medullary centres fail in the order, the respiratory centre, the vasomotor centre and, as an end-result, the cardiac centre. Moreover, it is observed that recovery from these non-volatile anæsthetics follows the same pattern as that observed during recovery from volatile anæsthetics.

When excessive dosage is used, the results produced are exactly similar to those which occur when overpressure is employed with volatile anæsthetics. Thus the rate of absorption and, in consequence, the speed with which anæsthetic depression is produced, are considerably accelerated; but it is significant that the response

fixation of the anæsthetic after it has been concentrated at the site of its drug fixation; or it may be due to other yet unknown factors. There is little doubt that non-volatile anæsthetics vary in the rate of their uptake by tissue cells. Thus, anæsthetic equilibrium is established between blood and the tissue cells of the whole body in about 30 minutes in the case of evipan, and in about 60 minutes in the case of sodium barbitone; the slow absorption of sodium barbitone is undoubtedly one factor responsible for its delayed response. When delay due to uptake was excluded, Pickford (1927) found that ethyl alcohol produced a response in 1·5 - 5 seconds after its concentration at the site of its drug fixation; but in the case of butyl chloral hydrate, Clark (1933) observed that response was delayed for 2 minutes. In this controlled work, the difference in the rate of response of these two narcotics can be attributed to the relatively slower fixation of butyl chloral hydrate. Kopannyi, Murphy and Krop (1933) and Brundage and Gruber (1937) have shown when sodium barbitone is injected intravenously in dogs, that about 75 per cent. of the drug injected leaves the blood stream within 1-2 minutes, and it can be assumed that the slow response of the body to the action of sodium barbitone is due not only to sluggish uptake but also to delayed fixation. And there may be other factors acting to produce a delayed response, for the cardiac glucosides are known to be rapidly fixed by the myocardium, but delay nonetheless occurs between drug fixation and cell response, and the cause of the delayed response is not known.

(While it is impossible to determine the cause of the delayed response of the body to certain non-volatile anæsthetics, it is probable that delay in uptake and fixation are dominant factors. Delay in uptake is due to the physical properties of the anæsthetic and delay in fixation may be due to the chemical constitution of the anæsthetic; in neither case can the technique of administration modify this inherent pharmacological property of a non-volatile anæsthetic.)

It is clear that anæsthetics with a delayed response are not suitable for use in clinical practice for the production of anæsthesia deeper than hypnosis. In the case of the slow acting group of non-volatile anæsthetics, the period of time between their entrance

order, and these four non-volatile anæsthetics comprise the *very rapidly acting* group of non-volatile anæsthetics.)

The body's response to the members of the next group, which is termed the *rapidly acting* group of non-volatile anæsthetics, is quite slow, relative to the group just discussed. Das (1940) observed in mice that a medium hypnotic dose of nembutal

TABLE 39.

THE RATE OF RESPONSE OF THE BODY TO THE SEVERAL NON-VOLATILE BLOOD-BORNE ANÆSTHETICS IN COMMON CLINICAL USE.

Slow Acting	Rapidly Acting	Very Rapidly Acting
Barbitone	Amytal	Paraldehyde
Sodium Barbitone	Ortal	Avertin
Dial	Pernocton	Evipan
Luminal	Scopolamine	Pentothal
	Nembutal	
	Morphia	

produced a state of hypnosis in about 5 minutes after its intravenous injection The other barbiturates of this group, cited in Table 39, show a delayed response of approximately the same order as that of nembutal. The body's response to scopolamine, injected intravenously is more rapid than that of nembutal, and that of morphia approaches the order of response of the very rapidly acting group.

The response of the body to the members of the next group of non-volatile anæsthetics, the *slow acting* group, is very much delayed. Das (1940) found that a medium hypnotic dose of sodium barbitone produced hypnosis in mice 22 minutes after its intravenous injection. The response of the body to barbitone is even more delayed while the remaining members of this group show a delayed response of about the same order as that of sodium barbitone

Delay in the biological response of the body to an anæsthetic injected intravenously may be due to sluggish uptake of the drug by tissue cells from circulating blood, it may be due to delayed

flowing through the organ, it follows that as the blood concentration of a non-volatile anæsthetic falls due to its deviation to non-nervous tissues and its excretion from the body, so the anæsthetic content of the brain is reduced. When at length the anæsthetic concentration in arterial blood, and in turn in the brain itself, has fallen below the minimum threshold concentration necessary to depress the brain, anæsthesia ceases.

The character of the clearance of narcotics from circulating blood has been investigated by Widmark and Tandberg (1924), who found that the clearance may be *constant* or *exponential* in character.

On the one hand, when a units of a narcotic enter circulating blood per unit time and b units of the narcotic are removed from circulating blood per unit time, then $(a-b)$ units of the drug accumulate in the blood per unit time. Narcotics whose clearance is constant may be safely used in clinical practice when a single hypnotic dose is administered, but when they are administered continuously, accumulation of the narcotic in circulating blood continues unabated until at length a lethal dose is achieved. The only narcotics which are known to conform to this constant rate of clearance are ethyl and methyl alcohol, and on this account they are not suitable for continuous administration in clinical anæsthetic practice.

On the other hand, when a units of a narcotic enter the blood stream per unit time, and a constant fraction of this amount, $\frac{1}{b}$ units of narcotic, are removed from the blood stream per unit time, then the narcotic accumulates in circulating blood until the rate of clearance equals the rate of entrance. This occurs when ab units of the narcotic have accumulated in circulating blood, and if the rate of intake remains constant, *no further increase in the blood concentration of the narcotic can occur.* This form of clearance is exponential in character, and a fixed proportion—not a fixed amount—of the narcotic is cleared per unit time from circulating blood. When this type of clearance obtains, the greater the concentration of a narcotic in circulating blood, then, within limits, the greater will be the mass of narcotic cleared from it per unit time. In single-dose administration, this form of clearance gives the greatest possible protection from narcotic overdose, but

into circulating blood and the biological response makes it quite impossible for the anæsthetist to use the subject's reaction to the anæsthetic as a guide to its administration; and the slow acting non-volatile anæsthetics are used clinically in single hypnotic doses. The relatively slow response of the body to the rapidly acting group of non-volatile anæsthetics makes it difficult to judge the dose of these anæsthetics to the reaction of the subject during its administration. From 1930-3, members of the rapidly acting group, such as nembutal and pernocton, were extensively used in this country in clinical practice by intravenous administration to produce surgical anæsthesia, and they were injected intravenously at the rate of 1 c.c. of a 10 per cent. solution per minute, in order to assess accurately the response of the subject to their action during their administration. The intravenous administration of these rapidly acting barbiturates was abandoned as soon as the very rapidly acting barbiturates, evipan and pentothal, became available, and nowadays the rapidly acting non-volatile anæsthetics are used only in single hypnotic doses. The response of the body to the members of the very rapidly acting non-volatile anæsthetics is such that they may be safely used in clinical practice in greater than hypnotic doses Paraldehyde and avertin, absorbed from the rectum, are used as basal anæsthetics. Evipan and pentothal may be safely used intravenously to produce surgical anæsthesia, for the response of the subject to these anæsthetics is so rapid that his reaction during anæsthesia can be used as a guide for their administration

With non-volatile just as with volatile anæsthetics, the level of anæsthetic depression produced depends on the concentration of the anæsthetic in circulating blood, and as long as an effective concentration of an anæsthetic is maintained in the cerebral capillaries, so long will anæsthesia continue. If the concentration of a non-volatile anæsthetic in circulating blood depended solely on the mass of the anæsthetic administered per unit time, the limitations of particular non-volatile anæsthetics described above would obtain, but this takes no heed of the character and the rate at which non-volatile anæsthetics are *cleared* from circulating blood. Since no organ of the body can maintain a greater concentration of anæsthetic than its concentration in arterial blood

circulatory system is less than that of the first round, and during this second round, pentothal is again absorbed by the brain and other nervous and non-nervous tissues, and the same fraction of its contained pentothal is again rendered inert by detoxication. The uptake and fixation of pentothal by the brain is rapid, and maximum anæsthesia with pentothal is achieved in about 60 seconds. In this instance, it can be assumed that equilibrium in respect to pentothal has been attained between the brain and arterial blood in about 60 seconds—that is, after two rounds of blood. It has been concluded that the uptake of pentothal by the brain is more rapid than that of any other type of body tissue, and it can be assumed that the pentothal content of mixed venous blood at the end of this second round of the circulatory system is less than that of the brain, but is greater than that of all other types of nervous and non-nervous tissue cells. Consequently, arterial blood setting out on its third round of the circulatory system has a pentothal content less than that of the brain, but greater than that of all other types of nervous and non-nervous tissues. It follows, during the third round of the circulatory system, that blood *will gain* pentothal from the brain, and the level of anæsthetic depression will be correspondingly diminished, but it *will lose* pentothal to all other types of nervous and non-nervous tissues, and, moreover, the same proportion of its contained pentothal will be again rendered inert by detoxication. On balance, the pentothal content of mixed venous blood returning to the right heart at the end of this third round of blood, and in consequence, the pentothal content of arterial blood setting out on its fourth round of the circulatory system, is again reduced, relative to the preceding round. And with each successive round of blood, the concentration of pentothal in arterial blood—and, in turn, in the brain—falls, as the redistribution between blood, brain and other nervous and non-nervous tissues and the detoxication of pentothal proceeds: at length, about 30 minutes after its intravenous injection, equilibrium in respect to pentothal has been assumed throughout the whole body. The uptake of pentothal by body tissue other than the brain is thus an important aid in the clearance of non-volatile anæsthetics from circulating blood, and the mass of non-volatile anæsthetic cleared from circulating blood

when continuous administration is employed, *this form of clearance is an indispensable requisite to the safe administration of the narcotic in clinical anæsthetic practice.*

The clearance of the volatile anæsthetics in common clinical use from the blood stream by lung ventilation has been seen to be exponential in character, and the excretion coefficient of the individual volatile anæsthetic represents the constant fraction of the mass of anæsthetic present which is cleared from circulating blood per unit time. Evipan, pentothal, avertin, paraldehyde and nembutal are known to be cleared from circulating blood exponentially, and, ignoring all other factors, these non-volatile anæsthetics are therefore suitable for use in clinical anæsthetic practice by continuous administration. Das (1940) estimated in mice that 1/28 - 1/35th part of the evipan content of circulating blood was cleared per minute. In the case of pentothal, the constant fraction cleared was 1/40 - 1/50th, and in the case of nembutal, it was 1/60 - 1/80th part per minute. So far as the rate of clearance of non-volatile anæsthetics influences the safety of their clinical administration, evipan is the safest, and then in order, pentothal and finally nembutal. Clinical experience suggests that the excretion coefficient of pentothal in Man is equal to or greater than that of evipan.

The mechanism of the clearance of non-volatile anæsthetics, such as evipan or pentothal, from circulating blood is a dual one. It can be illustrated by considering the fate of a single effective dose of pentothal injected intravenously.

During the first round of blood through the circulatory system after the intravenous injection, a proportion of its contained pentothal is carried to and absorbed by the brain; a proportion is carried to and absorbed by other nervous and non-nervous tissues; and a proportion is rendered inert by detoxication prior to its excretion from the body Mixed venous blood therefore returns to the right heart after this first round of blood with its pentothal content depleted by the mass of pentothal absorbed by the brain and other nervous and non-nervous tissues *plus* the mass of pentothal rendered inert by detoxication On this account, the pentothal content of arterial blood setting out on its second round of the

in the urine by the kidneys, and in part as degraduation products after detoxication by the liver.

Non-volatile anæsthetics which are detoxicated in the body prior to the excretion of their degradation products are termed *reactive anæsthetics*, for they are excreted from the body in forms other than that in which they were absorbed, and reactive anæsthetics are detoxicated in a variety of ways. Oxidation and conjugation are the most common mechanisms of detoxication: primary and secondary alcohols are oxidised to their corresponding acids, while tertiary alcohols and the halogen substitution alcohols (such as avertin and trichlorethyl alcohol which are resistant to oxidation) are conjugated probably with glycuronic acid to form harmless glycuronates which are then excreted in the urine by the kidneys. Hydrolysis is also a common form of detoxication: alkaloids, such as scopolamine and atropine, are hydrolysed in part at least to their corresponding acids prior to their excretion in the urine. Reduction is a less common form of detoxication: chloral hydrate is reduced to trichlorethyl alcohol, which is then conjugated with glycuronic acid. Deamination is an intermediate step in the detoxication of amines, and methylation is a rare form of detoxication.

The detoxication of a reactive non-volatile anæsthetic is usually a rapid process. Barbiturates with complex cyclic radicals and side-chains—such as evipan, ortal and nembutal—and thio-barbiturates—such as pentothal—are relatively labile compounds, and they undergo rapid side-chain oxidation in the body. Lundy and others cast a wide net and believe that tissues other than the liver are responsible for the detoxication of reactive non-volatile anæsthetics. There is no reason to doubt that this is possible, but it may be inferred from the following evidence that the liver is the organ mainly responsible for the detoxication of reactive non-volatile anæsthetics and is, in fact, *the obligatory route* for their detoxication in clinical anæsthetic practice.

Pratt (1933) produced liver damage in rabbits by the administration of carbon tetrachloride and phosphorus, sufficient to impair the animals' ability to excrete bromsulphalein, and he observed that these animals were very susceptible to the action of nembutal. Cameron and de Saram (1938) verified these observations in rats

in this fashion is said to be *deviated* to non-nervous tissues and nervous tissues other than the brain.

The deviation of non-volatile anæsthetics is most rapid in the period immediately following intravenous injection, when the diffusion gradient between blood and the tissues is high; and it decreases in a logarithmic manner to reach the limit of its usefulness *when equilibrium in respect to the non-volatile anæsthetic* has been assumed between blood, brain and other nervous and non-nervous tissues. In the case of evipan and pentothal, this occurs about 30 minutes after their intravenous injection. The deviation of non-volatile anæsthetics to non-nervous tissues is thus a very material aid to the clearance of these anæsthetics from the blood stream, and is most effective immediately after intravenous injection, when the risk of depression of the vital medullary centres are most likely to occur. Deviation to non-nervous tissues, however, is not a means of inactivating non-volatile anæsthetics or eliminating them from the body. When the mechanism of excretion of non-volatile anæsthetics, such as nembutal, is sluggish and/or faulty, Cameron (1939) has shown, in mice, that the deviation of slow acting barbiturates to non-nervous tissues does not provide for the clearance of sufficient anæsthetic from the blood stream to prevent overdose. The author has records of six deaths, and more than a score of cases in which anæsthesia lasted from 5 - 22 hours, after the intravenous injection of pentothal 0 5 grams in soldiers suffering from liver inefficiency due to various tropical diseases. And there is little doubt that deviation of non-volatile anæsthetics to non-nervous tissues is an aid to their clearance from circulating blood, but that the excretion of these anæsthetics from the body is the dominant factor concerned with their clearance from circulating blood.

The physical state of non-volatile anæsthetics prevents their elimination from the body through the medium of the respiratory system, and they are excreted from the body in two ways. Certain non-volatile anæsthetics are detoxicated in the liver prior to the excretion of their harmless degradation products in the urine by the kidneys. Others are excreted by the kidneys unchanged, in the same form as that in which they were absorbed, and many non-volatile anæsthetics are excreted in part, unchanged

most typical non-reactive non-volatile anæsthetic in common clinical use is barbitone, a stable barbiturate with short side-chains; after its oral administration in Man, up to 80 per cent. of the ingested drug can be recovered unchanged in the urine.)

That the kidneys are the obligatory route for the excretion of non-reactive non-volatile anæsthetics is shown by the following evidence. Pratt (1933) and Cameron and de Saram (1938) have shown that experimental hepatitis does not interfere with the normal excretion of barbitone. Hirschfelder and Haury (1933) have shown in nephrectomized rabbits, and Murphy and Koppanyi (1934) in dogs, cats and rabbits with severe experimental nephritis, that barbitone or luminal, in doses sufficient to allow recovery in a normal animal in 11-13 hours, is followed in these nephropathetic animals by anæsthesia prolonged much beyond these limits and/or by death of the animal. The renal excretion of non-reactive, non-volatile anæsthetics is slow. Thus, after a hypnotic dose of barbitone in a normal man, 8 per cent. of the ingested drug was excreted in the urine in the first 12 hours, 20 per cent. in the first 24 hours—65 per cent. during the first forty-eight hours, and traces of barbitone were still detectable in the urine 9 days after its administration. This slow rate of excretion accounts for the long duration of action of the stable, non-reactive, non-volatile anæsthetics with short alkyl radicals such as barbitone, whose obligatory route of excretion is the kidneys.

Many non-volatile anæsthetics, however, are excreted in the urine by the kidneys, in part unchanged and in part as degradation products after detoxication in the liver. (After oral administration in man, 30 per cent. of dial, 25 per cent. of luminal and 3-8 per cent. of sodium amytal can be recovered unchanged in the urine, and there is reason to believe that the remainder is detoxicated in the liver.) Thus, Koppanyi, Dille and Krop (1936) have shown that rabbits and cats, given half the fatal dose of luminal twenty-four hours after recovery from chloroform anæsthesia lasting for two hours, remain deeply anæsthetised for long periods of time, and may even die. The abnormally powerful and prolonged response to such dosage can be attributed to faulty and sluggish detoxication of luminal because of liver damage produced by chloroform. When this result is coupled with the observations of

with liver damage produced by carbon tetrachloride, and found that the response of these animals to normal doses of evipan and nembutal was excessive both in respect to the intensity and the duration of action produced. They showed, moreover, when liver regeneration had occurred, that this susceptibility disappeared, but if, owing to progressive liver degeneration, the pre-cirrhotic stage was reached, then the response of the body to both these barbiturates was excessive. Brundage and Gruber (1937) have shown that the degradation products of the detoxication of amytal, ortal and nembutal appearing in the urine are narcotically inert; and they showed, moreover, that nephrectomised dogs recovered from ortal, a rapidly acting barbiturate, as rapidly as did normal animals. Hence, it can be inferred that the abnormally powerful and prolonged response observed by Pratt and by Cameron and de Saram was due to faulty and sluggish detoxication of these reactive non-volatile anæsthetics produced by liver inefficiency. This conclusion agrees with the results observed in clinical practice, for, as mentioned above, death of the subject, and/or anæsthesia lasting up to 22 hours, have occurred after the intravenous injection of as little as 0 5 grams of pentothal in soldiers with liver inefficiency. Ignoring all else, in clinical practice it is suggested that it is a wise convention to accept the liver as the main, if not the obligatory, route for the detoxication of reactive non-volatile anæsthetics, until conclusive evidence is obtained to the contrary.

Any anæsthetic which can diffuse through the capillary membrane appears in the urine, and few, if any, of the anæsthetics in common clinical use are completely re-absorbed in the renal tubules. Thus, volatile anæsthetics appear in the urine and the kidney provides an alternative method of excretion for reactive non-volatile anæsthetics such as pentothal, evipan, amytal, nembutal, etc ; but in each instance this method of excretion is much too slow to prevent the accumulation of the anæsthetic in circulating blood, and subsequent overdose. Certain stable non-volatile anæsthetics, however, escape destruction in the body, and are normally excreted in the urine by the kidneys, unchanged, in the same form as that in which they were absorbed. Such non-volatile anæsthetics are *non-reactive* in character, and the kidneys are the *obligatory route* for their excretion from the body. The

Codein is a predominantly non-reactive anæsthetic, for 80 per cent. of the injected dose is excreted unchanged in the urine by the kidneys. Scopolamine is more reactive than codein, for 33 per cent. of the injected dose is excreted unchanged by the kidneys,

TABLE 40.

THE PATTERN OF THE EXCRETION OF THE SEVERAL NON-VOLATILE BLOOD-BORNE ANÆSTHETICS IN COMMON CLINICAL USE.

Non-reactive	Predominantly non-reactive	Predominantly reactive	Reactive
Barbitone Heroin	Codein Scopolamine Dial Luminal Morphia	Sodium Amytal Ortal Nembutal Pernocton Paraldehyde Avertin	Evipan Pentothal

and the remainder is detoxicated by the liver. Dial and luminal are still more reactive, for 30 per cent. of dial and 25 per cent. of luminal is excreted unchanged by the kidneys, while the remainder is detoxicated by the liver. Morphia has the most rapid excretory rate of the members of this group, for 10 per cent. of the morphia injected is excreted within four hours, unchanged in the urine by the kidneys, and the remaining 90 per cent. is detoxicated by the liver. The relatively slow excretion of morphia indicates the even slower rate of excretion of the other members of this group, and in general, as the proportion of anæsthetic excreted by the kidneys increases, so the rate of excretion of the members of this group of non-volatile anæsthetics decreases. In clinical practice, the more non-reactive members of this group, such as codein and scopolamine, must be used with caution when renal inefficiency is present, and with the more reactive members, such as morphia, liver inefficiency engenders caution.

Only 3-8 per cent of the mass of sodium amytal administered can be recovered unchanged in the urine, and the remainder is

Murphy and Koppanyi already cited, it can be concluded that about 25 per cent. of the luminal absorbed is excreted unchanged by the kidneys, and the remainder is rendered inert by detoxication in the liver. The members of this group of non-volatile anæsthetics can be classified as *predominantly non-reactive* or *predominantly reactive*, and it can be taken as a general principle that the greater the proportion of a non-volatile anæsthetic detoxicated by the liver, the more rapid will be its rate of excretion from the blood stream

It is clear that each member of the barbiturate group of non-volatile anæsthetics is excreted from the body in its own characteristic fashion, and the barbiturates in common clinical use may be divided into four groups according to the character of their excretion from the body. Reactive barbiturates such as evipan and pentothal, are wholly detoxicated by the liver, and the rate of their clearance from circulating blood approaches that of the volatile anæsthetics and is very rapid. By far the greater proportion of amytal, ortal, nembutal and pernocton is detoxicated by the liver, and these barbiturates, which are predominantly reactive, are cleared from circulating blood rapidly. As the proportion of barbiturate detoxicated by the liver becomes smaller, as in luminal and dial, the rate of their clearance from the blood stream becomes slower, and these barbiturates are classified as predominantly non-reactive in character. Finally, barbitone which is excreted almost wholly by the kidneys is termed a non-reactive anæsthetic, and the rate of its excretion is very slow.

The various other non-volatile anæsthetics in common clinical use follow the pattern of the excretion of the barbiturates, and they may be classified according to the mechanism of their excretion into these same four groups. The non-volatile blood-borne anæsthetics in common clinical use are classified in this fashion in Table 40, and the members of each group are tabulated with the anæsthetic whose excretory rate is slowest at the top of the column, and then in order as the rate of excretion increases.

Barbitone and heroin are non-reactive anæsthetics excreted almost wholly unchanged in the urine by the kidneys. When renal inefficiency is present, these non-volatile anæsthetics must be used with caution.

abnormally intense and prolonged. In clinical practice, the members of this predominantly reactive group of non-volatile anæsthetics must be used with care and clinical acumen when liver inefficiency is present or is suspected.

Evipan and pentothal are reactive anæsthetics, and are detoxicated almost wholly in the body by the liver. They are excreted from circulating blood more rapidly than any other non-volatile anæsthetic in common clinical use, and the rate of their excretion approaches that of the volatile anæsthetics. When liver inefficiency is present or is suspected, they should not be used in clinical practice, for detoxication by the liver is the obligatory route of their excretion.

All the non-volatile anæsthetics in common clinical use are potent narcotics, and it is possible to administer clinically a fatal dose with each of these anæsthetics. In classifying them according to the pattern of their behaviour and the field of their clinical usefulness, the dominant characteristics chosen to differentiate them are: the sequence of the biological response of the body to their action, the rate at which this response is produced, and the rate of their excretion from circulating blood. These qualities of the non-volatile anæsthetics in common clinical use are shown in Table 41, and they permit these anæsthetics to be divided into three broad groups.

The non-volatile anæsthetics of the first group are used in clinical practice as pre-anæsthetic medicants in single hypnotic dosage. As Table 41 shows, they fall naturally into three subgroups.

The response of the body to non-volatile anæsthetics such as barbitone, sodium barbitone, ipral, chloral hydras, dial, and perhaps luminal, whose oil/water partition coefficients are less than unity, is similar to that of alcohol and acetone, and is not the standard safe sequence of response. On this account, these anæsthetics must be used in hypnotic dosage if they are to be used safely, and this is the more necessary since the body's rate of response is a very delayed one. The rate of their excretion from the body is very slow; because of this, accumulation of these anæsthetics may readily occur when repeated doses are given or when they are administered continuously. This danger is accentuated

detoxicated by the liver. Ortal, nembutal and pernocton are regarded as predominantly reactive substances which are detoxicated almost entirely by the liver. They have not been studied quantitatively regarding their renal excretion, but the rate of their excretion in clinical practice indicates that the proportion of these anæsthetics excreted in the urine by the kidneys is less than that of sodium amytal. Paraldehyde is also a predominantly reactive anæsthetic. The observations of Levine, Gilbert and Bodansky (1939) indicate that paraldehyde is detoxicated in the liver, for prolonged narcosis and raised blood paraldehyde curves were obtained in dogs with liver degeneration produced by chloroform A small proportion of the paraldehyde administered, however, escapes destruction in the liver; and of this, the greater part is excreted unchanged by the lungs, and the smaller part is excreted unchanged in the urine by the kidneys. Its rate of excretion is rapid, and excretion in expired air adds to the safety of its administration Avertin, the last member of this group, is a reactive anæsthetic which might well have been classified with the reactive non-volatile anæsthetics. It is conjugated with glycuronic acid in the liver, and its degradation product, avertin glycuronate, is excreted quantitatively in the urine by the kidneys. Goodman and Gilman (1942), however, state that if renal function is poor, excretion may be considerably delayed and the toxicity of avertin correspondingly enhanced This suggests either that avertin is not a predominantly reactive anæsthetic, or that the product of its dissociation, avertin glycuronate, is an active narcotic. Straub (1931) states that 80 per cent. of the avertin injected can be recovered as avertin glycuronate in the urine, and avertin is, therefore, a predominantly reactive substance. Maddox (1931) states that double nephrectomy in dogs produces little or no decrease in the normal detoxication time of avertin, and it follows that avertin does not depend upon renal excretion, and that avertin glycuronate, which does depend upon renal excretion is not narcotically an active substance. This is in accord with clinical experience of this anæsthetic since 1930, for when in the absence of liver inefficiency avertin was used as a basal anæsthetic in 632 cases in urological practice, no signs of accumulation were observed. In the presence of liver inefficiency, however, the response to basal dosage is

when renal inefficiency is present.) It follows that in clinical anæsthetic practice these non-volatile anæsthetics must be used in *single hypnotic dosage* and they are best administered by mouth.

The data available indicate that the remaining non-volatile anæsthetics cited in Table 41 have an oil/water partition coefficient of more than unity and less than 6 (circa). On this account, it is expected that the body's response should be the standard response, and clinical experience suggests that this is so in fact. The body's response to amytal, ortal, pernocton and nembutal, however, is fairly slow, and this makes the subject's reactions during the uptake of these anæsthetics an inaccurate guide for their administration. When to this is added the slow excretory rate of these anæsthetics, it is clear that accumulation may readily occur, and that overdose can readily be produced unless they are used in single dosage. The danger of accumulation and subsequent overdose is increased when liver inefficiency is present, for they are predominantly reactive anæsthetics. For these several reasons, these non-volatile anæsthetics are given by mouth, by rectum or intravenously in *single hypnotic dosage*, if they are to be used safely. Since they are tissue irritants, they should not be injected subcutaneously or intramuscularly.

The response of the body to heroin, codein, scopolamine and morphia is the standard response, and this response is produced fairly rapidly when these non-volatile anæsthetics are injected intravenously. When they are given by mouth or are injected subcutaneously or intramuscularly, the rate of response varies with the vascularity of the site of absorption, generally speaking, it is comparable with the rate of response of the first sub-group. The rate of excretion of heroin, codein and scopolamine is very slow, and is further delayed when renal inefficiency is present. By contrast, the rate of excretion of morphia is more rapid, but relative to pentothal and the volatile anæsthetics, the rate of excretion of morphia is slow, and is further delayed when liver inefficiency is present Because of the rate of response of the body to their action and because of their excretion rate, these non-volatile anæsthetics are administered in *single hypnotic dosage* by mouth, or subcutaneously, intramuscularly or intravenously.

It can be concluded that the slow rate of excretion of the members of the first group of non-volatile anæsthetics makes the control

TABLE 41

THE PATTERN OF THE BEHAVIOUR OF THE SEVERAL NON-VOLATILE BLOOD-BORNE ANÆSTHETICS IN COMMON CLINICAL USE.

Non-volatile Anæsthetics	Standard Response	Rate of Response	Rate of Excretion	Administration in clinical practice	
Barbitone Sod. Barbitone Ipral Chloral hydras Luminal Dial	No No No No Yes ? No	Slow Slow Slow Slow Slow Slow	Very slow Very slow Very slow Very slow Very slow Slow	By mouth	IN SINGLE HYPNOTIC DOSE
Amytal Ortal Pernocton Nembutal	Yes Yes Yes Yes	Fairly slow Fairly slow Fairly slow Fairly slow	Slow Slow Slow Slow	By mouth, Intravenously or By rectum	
Heroin Codein Scopolamine Morphia	Yes Yes Yes Yes	Fairly rapid Fairly rapid Fairly rapid Fairly rapid	Very slow Very slow Very slow Slow	By mouth, subcutaneously, intramuscularly & intravenously	
Paraldehyde Avertin	Yes Yes	Rapid Rapid	Fairly rapid Fairly rapid	By rectum	IN SINGLE BASAL DOSE
Evipan Pentothal	Yes Yes	Very rapid Very rapid	Rapid Rapid	Intravenously by single or continuous administration	IN SURGICAL DOSAGE

when renal inefficiency is present.) It follows that in clinical anæsthetic practice these non-volatile anæsthetics must be used in *single hypnotic dosage* and they are best administered by mouth.

The data available indicate that the remaining non-volatile anæsthetics cited in Table 41 have an oil/water partition coefficient of more than unity and less than 6 (circa). On this account, it is expected that the body's response should be the standard response, and clinical experience suggests that this is so in fact. The body's response to amytal, ortal, pernocton and nembutal, however, is fairly slow, and this makes the subject's reactions during the uptake of these anæsthetics an inaccurate guide for their administration. When to this is added the slow excretory rate of these anæsthetics, it is clear that accumulation may readily occur, and that overdose can readily be produced unless they are used in single dosage. The danger of accumulation and subsequent overdose is increased when liver inefficiency is present, for they are predominantly reactive anæsthetics. For these several reasons, these non-volatile anæsthetics are given by mouth, by rectum or intravenously in *single hypnotic dosage*, if they are to be used safely. Since they are tissue irritants, they should not be injected subcutaneously or intramuscularly.

The response of the body to heroin, codein, scopolamine and morphia is the standard response, and this response is produced fairly rapidly when these non-volatile anæsthetics are injected intravenously. When they are given by mouth or are injected subcutaneously or intramuscularly, the rate of response varies with the vascularity of the site of absorption; generally speaking, it is comparable with the rate of response of the first sub-group. The rate of excretion of heroin, codein and scopolamine is very slow, and is further delayed when renal inefficiency is present. By contrast, the rate of excretion of morphia is more rapid, but relative to pentothal and the volatile anæsthetics, the rate of excretion of morphia is slow, and is further delayed when liver inefficiency is present. Because of the rate of response of the body to their action and because of their excretion rate, these non-volatile anæsthetics are administered in *single hypnotic dosage* by mouth, or subcutaneously, intramuscularly or intravenously.

It can be concluded that the slow rate of excretion of the members of the first group of non-volatile anæsthetics makes the control

of their blood concentration sluggish and inflexible, and the delayed response of the body to their action renders the signs of anæsthesia an inaccurate indication of the level of the brain's anæsthetic depression. For these two very pertinent reasons, repeated single dosage or continuous administration must be contra-indicated in the interest of safety. This is especially so in the case of non-volatile anæsthetics of the first sub-group, for the distorted sequence of response of the body to their action makes the early depression of the vital medullary centres an added danger when a greater hypnotic dosage is used. Nembutal, which is the most reactive member of the first group, has the most rapid excretory rate, and is frequently used by mouth in basal dosage. In the past, nembutal and pernocton were used intravenously in basal dosage, but this practice was abandoned when the very reactive non-volatile anæsthetic, evipan, was discovered. The members of this first group of non-volatile anæsthetics are most commonly employed in clinical practice as pre-anæsthetic medicants; when used for this purpose in single hypnotic dosage, they are safe and valuable adjuvants to a balanced anæsthetic.

The members of the second group of non-volatile anæsthetics, paraldehyde and avertin, are used in clinical anæsthetic practice by rectum as basal anæsthetics. The rate of their excretion from circulating blood is fairly rapid, and because of this, the control of their blood concentration is more flexible and exact than that of the members of the first group. Since the response of the body to their action is the standard one, this increased control of their blood concentration permits a deeper level of anæsthetic depression of the brain to be more safely produced in clinical practice with paraldehyde and avertin than with the non-volatile anæsthetics of the first group. When injected intravenously, the body's response to paraldehyde and avertin is rapid (but not so rapid as that of evipan, pentothal or the volatile anæsthetics), and it is fairly rapid when other methods of approach to the blood stream are employed. Although the control of their blood concentration is fairly exact and flexible, most anæsthetists agree that paraldehyde and avertin should be used in single basal dosage, for the time-lag between the presence of an effective concentration of these anæsthetics in circulating blood and the appearance of the signs of anæsthesia which correspond to this blood concentration makes the clinical

control of paraldehyde or avertin too inexact to protect the subject during deeper levels of anæsthesia. When liver inefficiency is present or is suspected, avertin is contra-indicated, while paraldehyde is less dangerous because this anæsthetic is excreted in part by the lungs. Clinical experience has shown that paraldehyde and avertin are most conveniently administered by rectum, and these non-volatile anæsthetics of the second group are therefore employed in clinical practice by rectum in single basal dosage.

The members of the third group of non-volatile anæsthetics, evipan and pentothal, are used in clinical anæsthetic practice by intravenous injection or by rectum for the production of basal anæsthesia; they are also used intravenously in single dosage or by continuous administration for the production of surgical anæsthesia.

The response of the body to evipan or pentothal is the standard safe sequence of response. The rate of their excretion from circulating blood in a healthy subject is very rapid, and this permits their blood concentration to be controlled by alterations in the rate of uptake, in an upward and a downward direction, in a manner comparable to, but not so flexible or rapid, as with volatile anæsthetics. The response of the body to alterations in the blood concentration of evipan or pentothal is very rapid; because of this, alterations of the blood concentration of evipan or pentothal are almost immediately followed by a corresponding change in the level of anæsthetic depression of the brain, and in consequence, by an almost immediate change in the clinical signs of anæsthesia. This permits the clinical signs of anæsthesia to be used as an accurate guide for the administration of evipan or pentothal in clinical practice, and any level of anæsthetic depression, short of medullary paralysis, can be safely produced clinically, by an experienced anæsthetist in a healthy subject. When, however, liver inefficiency is present or is suspected, evipan and pentothal must be used in single dosage with care and discrimination, *while their continuous administration must be considered a dangerous procedure.*

There is reason to believe that the uptake of non-volatile anæsthetics by the body cells from circulating blood is governed by the same factors governing the uptake of volatile anæsthetics; but the method of control of the blood concentration of non-volatile anæsthetics, and in turn the level of anæsthetic depression

produced by them, has little in common with the methods adopted in clinical practice for the control of volatile anæsthetics. In the first place, the method of approach of non-volatile anæsthetics to circulating blood is crude and inflexible when compared with the control afforded when volatile anæsthetics are dissolved in circulating blood through the medium of the respiratory system. Secondly, the anæsthetist has absolutely no control of the rate of excretion of non-volatile anæsthetics. He cannot hasten the rate of their excretion, and, moreover, disease, surgical shock, etc., may reduce the rate of excretion below normal limits. This is in marked contrast to the manner in which the anæsthetist can hasten or retard the rate of excretion of volatile anæsthetics. It follows that the control of the blood concentration of even the most flexible of non-volatile anæsthetics, pentothal, is crude and inflexible when compared with the control of the blood concentration of any of the volatile anæsthetics in common clinical use. Ignoring all other factors, it is for this reason that volatile anæsthetics are clinically safer than non-volatile anæsthetics. It is clear, too, that the mechanism of excretion of each non-volatile anæsthetic is largely responsible for the pattern of its clinical behaviour, the field of its clinical usefulness, and the method adopted to dissolve it in circulating blood; these factors combine to divide the non-volatile anæsthetics in common clinical use into three broad groups. It is proposed to discuss each group in terms of their method of approach to circulating blood, but it must be emphasised that a knowledge of the mechanism of the excretion of each non-volatile anæsthetic is essential for intelligent use in clinical practice.

References

1. Brundage, J. T., and Gruber, C. M. (1937). *J. Pharmacol* 60, 439.
2. Cameron, G. R., and de Saram, G. S. W. (1939). *J. Path. Bact* 48, 59.
3. Clark, A. J. (1933) "Mode of Action of Drugs on Cells." p. 36. Edward Arnold & Co., London.
4. Das, C. S. (1940) *Quart J. exp. Physiol* 30, 245.
5. Goodman, L., and Gilman, A. (1942) "The Pharmacological Basis of Therapeutics," p. 103. Macmillan, New York.
6. Hirschfelder, A. D., and Haury, V. G. (1933). *Proc. Soc exp. Biol N.Y.* 30, 1057.
7. Kopannyi, T., Dille, J. M., and Krop, S. (1936) *J Pharmacol.* 60, 439.
8. Levine, H., Gilbert, A. J., and Bodansky, M. (1939) *J. Pharmacol.* 67, 299.
9. Maddox, J. K. (1931). "An Introduction to Avertin Rectal Anæsthesia" p. 20. Angus & Robertson, Sydney.

10 Murphy, W. S., and Koppanyi, T. (1934). *J. Pharmacol.* 52, 70.
11. Pickford, L. M. (1927). *J. Physiol.* 63, 19.
12. Pratt, T. W. (1933). *J. Pharmacol.* 48, 285.
13. Tabern, D. L., and Shelberg, E. F. (1933). *J. Amer. chem. Soc.* 55, 328.
14 Weiss, S. (1936). *J. Amer. med. Ass.* 107, 2104.
(1936). *Int. Clin* 1, 36.
15. Widmark, E. M. P., and Tandberg, J. (1924). *Biochem. Z.* 147, 538.

CHAPTER XV

INTRAVENOUS ANÆSTHETICS

IN the past, a 90 per cent. solution of ethyl alcohol in glucose saline, a 5 per cent. solution of di-ethyl ether in normal saline and a variety of other anæsthetic solutions, have been used in clinical anæsthetic practice by intravenous administration for the production of surgical anæsthesia. Nowadays, only two non-volatile anæsthetics, evipan and pentothal, are commonly used in *clinical practice by the intravenous method of approach.* Occasionally avertin and morphia are used by intravenous injection, and chloral hydrate is employed intravenously in veterinary practice.

Since the walls of veins are relatively insensitive, and because solutions injected intravenously are rapidly diluted, the intravenous method of approach may be the only means of dissolving irritating or hypertonic solutions, such as the arsphenamines, in circulating blood without trauma. Certain standard solutions of non-volatile anæsthetics have proved to be irritants. Thus the extravascular injection of a 10 per cent. solution of pentothal may produce extensive destruction of soft tissues, and after its intra-arterial injection, gangrene has been reported in the tissues served by the artery into which the injection has been made; but the *intravenous injection of this solution produces no reaction* of a harmful nature in a healthy vein. The intravenous injection of a 10 per cent. solution of pentothal into an unhealthy vein sometimes produces thrombosis, but weaker solutions—viz. 5 per cent. and 2½ per cent—seldom, if ever, do so. It is important to realize that any solution, even normal saline, injected into the cephalic vein, often produces shoulder pain of a transitory nature, but no unpleasant or dangerous after-effects.

In suitable dilution, therefore, any narcotic whose uptake and fixation ensures that the body responds rapidly in the standard sequence to an effective concentration of the narcotic in circulating blood, and whose clearance from the blood stream is exponential

in character and very rapid, is suitable for use by continuous intravenous administration to produce surgical anæsthesia in clinical anæsthetic practice. As has been seen, only the volatile anæsthetics in common clinical use and the non-volatile anæsthetics, evipan and pentothal, completely satisfy these conditions. Nothing is gained—and a great measure of control is lost—when volatile anæsthetics are injected intravenously, for the inhalation method of approach to circulating blood permits volatile anæsthetics to be dissolved in circulating blood more flexibly and exactly than by any other method. To administer di-ethyl ether or any other volatile anæsthetic liquid intravenously, therefore, has no point. Since ethyl alcohol, methyl alcohol and chloral hydrate have an oil/water partition coefficient of less than unity, their intravenous administration in greater than hypnotic dosage must be condemned because of the possibility of a distortion of the standard response of the body to their action, with early depression of the vital medullary centres. This danger is accentuated in the case of ethyl alcohol, for its clearance from circulating blood is constant in character, and accumulation of this narcotic in circulating blood may readily occur. Methyl alcohol must be condemned for the same reason; in addition, the degradation products of its oxidation in the body are toxic, and methyl alcohol must be considered a noxious substance, unsuitable for use in clinical anæsthetic practice. Although both avertin and paraldehyde have been used by continuous intravenous administration for the production of surgical anæsthesia, most anæsthetists would agree that this is not a safe procedure, for the response of the body to their action is a delayed one, and the rate of their excretion is slow, relative to evipan, pentothal or the volatile anæsthetics. Unless the rate of intravenous injection is slow, the delayed response of the body to their action makes the subject's reactions during injection an inaccurate guide for their administration. Overdose may therefore readily occur, and, in this event, the relatively slow rate of their excretion makes it difficult if not impossible to correct the error in the limited time available. The response of the body to the action of all the remaining non-volatile anæsthetics in common clinical use, and the rate of their excretion, are slower even than that of avertin; they are, therefore, not suitable for continuous intravenous administration in clinical anæsthetic practice. In the past, morphia

has been used by continuous intravenous administration for the production of surgical anæsthesia, but it is difficult to discover any justification for its use as a maintenance anæsthetic; for, although the response of the body to morphia injected intravenously is rapid, its slow rate of excretion renders it a thoroughly dangerous anæsthetic when used by continuous intravenous administration. It can be concluded that the only anæsthetics which can now be considered suitable for use in clinical anæsthetic practice by continuous intravenous administration are evipan and pentothal.

These same conditions also determine whether an anæsthetic is suitable for the production of surgical anæsthesia by single-dose intravenous administration: once again, evipan and pentothal are the only anæsthetics in common clinical use which completely fulfil the conditions. In contrast to their continuous intravenous administration, the safety of these anæsthetics is considerably enhanced when they are used intravenously in single dosage, for the concentration of the anæsthetic in systemic blood reaches a maximum value immediately after the completion of the intravenous injection, and subsequent increase is impossible. On the contrary, the concentration of the anæsthetic in circulating blood immediately begins to fall, partly as the result of deviation to non-nervous tissues, and partly as the result of detoxication.

The deviation of the anæsthetic to non-nervous tissues meets the first shock of this high initial concentration and is most rapid just when it can be of most use This is in the period immediately following intravenous injection, when the diffusion gradient between blood and non-nervous tissues is high: and the greater the rate of uptake of the particular non-volatile anæsthetic from circulating blood to tissue cells, the greater the rate of clearance of the anæsthetic from circulating blood by deviation to non-nervous tissues. In the case of evipan and pentothal deviation to non-nervous tissues is rapid and reaches the limit of usefulness in about thirty minutes after intravenous injection.

The rate of detoxication of evipan and pentothal is also very rapid, and this affords the greatest measure of protection against inadvertent overdose. The character of detoxication of these two anæsthetics is exponential, and, within limits, the greater the initial blood concentration following intravenous injection, the greater

will be the mass of these anæsthetics detoxicated at each round of blood through the circulatory system.

Because of the very rapid clearance of evipan and pentothal from circulating blood in the period immediately following intravenous injection, single-dose intravenous administration of these anæsthetics in a healthy subject can be carried to the level of depression of the respiratory centre without danger, if anoxia is avoided. Hence evipan and pentothal are in common clinical use by single-dose intravenous injection for the production of anæsthesia ranging from hypnosis, as used in psychiatric abreaction, to the level of anæsthetic depression required for a complete manipulation in orthopædic surgery.

Because accumulation cannot occur in single-dose intravenous administration, non-volatile anæsthetics which produce a rapid response may be used intravenously in single hypnotic dosage as pre-anæsthetic medicants. As pre-anæsthetic medicants their action should be relatively prolonged: a non-volatile anæsthetic which produces a rapid response, but whose excretion is exponential in character yet relatively slow, is required. Morphia and scopolamine fulfil these requirements, and when 0·2 milligrams of morphia or 0·004 milligrams of scopolamine per kilo of body weight, suitably diluted, are injected intravenously with due regard to the reactions of the particular subject, a state of deep hypnosis is safely produced in a healthy subject in from 15 - 30 seconds.

The inexpensive equipment required to perform an intravenous injection, the ease with which it can usually be made, and the absence of unpleasant subjective symptoms during the intravenous injection of narcotics, have popularised the use of evipan and pentothal in clinical anæsthetic practice. It must be conceded that evipan and pentothal are amongst the safest of anæsthetics when used with care and discrimination in normal subjects; but reference to Table 42 shows that during the first decade of their clinical history, they proved to be from four to five times more lethal even than chloroform. Since everything we know of evipan and pentothal indicates that they are, *per se*, safe and reliable anæsthetics, one is forced to conclude that this deplorable result must be attributed mainly to mal-administration resulting from a failure by anæsthetists to understand the principles which govern the intake and excretion of these non-volatile anæsthetics.

TABLE 42.

MORTALITY COMPARED FOR VARIOUS ANÆSTHETICS.

Anæsthetic	Mortality	Authority
Evipan	1 death per 813 cases	German, Auschutz, 1933
Evipan	1 death per 909 cases	French, Menegaux and Sechehage, 1934
Evipan	1 death per 748 cases	South African, 1936
Pentothal	1 death per 714 cases	Australian, Morton, 1942
Chloroform	1 death per 3,500 cases	American, Gwathmey, 1912 quoted from Sollmann.
Ethyl Chloride	1 death per 7,000 cases	
Di-ethyl ether	1 death per 15,000 cases	
Nitrous oxide	1 death per 5,000,000 cases (dental cases)	

If mal-administration is, in fact, the reason for the high mortality rate of evipan and pentothal shown in Table 42, there is ample excuse for the detailed description of the intravenous administration of these non-volatile anæsthetics which follows below.

In clinical practice, both evipan and pentothal are injected intravenously in single dosage as a 10 per cent. solution in sterile distilled water, and each 10 c.c. of this standard solution contains one gram of the barbiturate. In the interest of greater control, and because a 10 per cent. solution is likely to produce tissue irritation when inadvertently injected extravascularly, evipan and pentothal are now commonly used in more dilute solutions, viz. 5 per cent. and 2½ per cent. solutions. Pentothal is also employed in a 0 3 - 1 per cent. solution in normal saline as an intravenous drip for continuous administration.

When a standard solution of pentothal is used in clinical practice as a continuous intravenous drip, the mass of pentothal entering the blood stream per unit time varies as the rate of drip. Since clearance is exponential in character, pentothal accumulates in circulating blood until the rate of entrance equals the rate of clearance; and from this time onwards, there is no further increase in the blood concentration of pentothal. The concentration of pentothal in circulating blood, and in turn the level of anæsthetic depression produced, can, therefore, be varied as the rate of drip of this standard solution.

When, however, a single dose of a standard solution of pentothal is injected intravenously, it is not sufficiently realized that the concentration of the anæsthetic in circulating blood at the end of the injection, and in turn the depth of anæsthesia produced by it, is determined mainly by *the speed with which the injection of this standard solution is made.* Suppose, for the purpose of description, that the rate of blood-flow through the vein selected for venepuncture is 200 c.c. per minute. If 10 c.c. of the standard 10 per cent. solution of pentothal is injected into this vein in 60 seconds, one gram of pentothal is mixed with 200 c.c. of venous blood, and a 0 5 per cent. (circa) solution of pentothal in venous blood flowing to the right heart results. When 10 c.c. of this same standard solution is injected into this same vein in 30 seconds, a 1 per cent. (circa) solution of pentothal in venous blood is produced,

TABLE 42

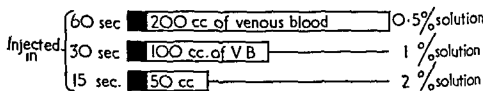
MORTALITY COMPARED FOR VARIOUS ANÆSTHETICS.

Anæsthetic	Mortality	Authority
Evipan	1 death per 813 cases	German, Auschutz, 1933
Evipan	1 *death* per 909 cases	French, Menegaux and Sechehage, 1934
Evipan	1 death per 748 cases	South African, 1936
Pentothal	1 death per 714 cases	Australian, Morton, 1942
Chloroform	1 death per 3,500 cases	American, Gwathmey, 1912 quoted from Sollmann.
Ethyl Chloride	1 death per 7,000 cases	
Di-ethyl ether	1 death per 15,000 cases	
Nitrous oxide	1 death per 5,000,000 cases (dental cases)	

pupil which reacts to light. Breathing is shallow and regular, the pulse rate is normal, and the pulse pressure may have fallen by about 10 mm. of mercury. Voluntary muscles are usually flaccid, but they possess muscle tone, and in response to external stimulation, muscles may contract spasmodically as, for example, when an attempt to introduce an airway produces masseter or laryngeal spasm. The response of the subject at the end of this 30-second pause, and particularly the speed with which the sulphur taste and the repetition of a particular number occurs, permit the anæsthetist to classify the subject's reaction to the 0 2 grams of pentothal which has been injected, as "normal," "resistant" or "susceptible." The reaction indicates not only the additional amount of pentothal which must be injected to produce a given level of anæsthetic depression, but also the speed with which the injection of this additional amount should be made, if the desired level of anæsthetic depression is to be produced. At the end of this 30-second pause, the injection of this 5 per cent. solution of pentothal is re-commenced, in susceptible subjects slowly, in normal subjects at about the same rate as heretofore, and in resistant subjects at a relatively rapid rate. Once again, preconceived notions are checked by the response of the subject during the intravenous injection of this additional amount. The pupils soon cease to react to light, and so indicate that the areas of sensory co-ordination of the brain are now depressed. Almost at the same time, the rigid arm into which the injection is made becomes flaccid, the jaw relaxes and the tongue may fall back and obstruct the airway. Breathing may now be so shallow that the volume of lung ventilation is insufficient to oxygenate the subject adequately. At this point, therefore, it is a wise precaution to insert a short airway and increase the oxygen pressure in inspired air to as much as 760 mm. of mercury, for if the depressing effects of anoxia are added to this level of anæsthetic depression, secondary cardiac failure may rapidly occur. At this point, too, a clear distinction should be drawn between very shallow breathing with an adequate circulatory rate and very shallow breathing with an appreciable fall of pulse pressure. In the first case, the respiratory centre is depressed by anæsthetic overdose, but the vasomotor centre and the cardiac centre are intact and active; if the circulation is maintained within normal limits with adequate oxygenation, the rapidity

and if the injection of this same mass of pentothal is completed in 15 seconds, one gram of pentothal is mixed with 50 c.c. of venous blood and a 2 per cent. (circa) solution in venous blood results Since the concentration of pentothal in this venous blood determines its concentration in mixed venous blood and, in turn, that

THE INFLUENCE OF THE RATE OF INTRAVENOUS INJECTION ON THE BLOOD CONCENTRATION OF PENTOTHAL



■ Represents 10 cc. of a 10% solution or 1 gram of pentothal

FIGURE 11.

of arterial blood entering the systemic circulation, it follows, when a single dose of a standard solution of pentothal or evipan is injected intravenously, that the speed with which the injection is made is the dominant factor determining the level of anæsthetic depression produced. This is shown diagramatically in Figure 11.

The usual method of administration of a single dose intravenous injection of pentothal is as follows:

The subject is instructed to count at a normal speed, and venepuncture having been successfully performed, 4 c.c. of a 5 per cent. solution of pentothal are injected in about 15 seconds and the injection is then interrupted for a period of about 30 seconds. Since a complete round or passage of the whole volume of blood through the circulatory system takes about 30 seconds, the rapid uptake of pentothal by the brain from circulating blood ensures that the reaction of the subject at the end of this 30-second pause is an accurate measure of his response to the 0·2 grams of pentothal which has been injected. The first response of the subject is often a taste of sulphur in the mouth, and this is followed by the repetition of a particular number, say, sixteen - sixteen - sixteen. In subjects with a normal average resistance to pentothal, repetition occurs when they have counted as far as 16 - 25, that is, in about twenty seconds Consciousness is lost within a few seconds of this repetition, and the eyeball assumes a central position, with a small

complete sensory loss is produced by single-dose administration as described above; with the needle, which should be of relatively large bore, still in the vein, the eccentric nozzle syringe is strapped to the forearm, or otherwise retained in position by one of the many devices available, such as Magill's third hand. One to two cubic centimetres of a 5 per cent. or 2½ per cent. solution of pentothal are then injected intravenously from time to time, in accord with the clinical condition of the subject and the needs of the surgical procedure. The same result may be achieved by inserting the needle of the pentothal syringe directly into the rubber tubing of a normal saline intravenous drip. With this method there is a certain time lag between injection and response; it can be materially reduced by inserting the needle of the syringe into the rubber tubing of the drip as closely as possible to the intravenous needle, and compressing the tube on the distal side of the syringe during injection. Since pentothal forms a precipitate with glucose, blocked needles are to be expected when glucose saline is employed for this form of administration.

When continuous intravenous administration is employed, pentothal is added in appropriate amounts to a stock transfusion bottle containing one pint of normal saline. Each additional half gram of pentothal added to one pint of saline increases its pentothal content by 0·1 per cent. (circa). Thus, 1½ grams of pentothal per pint make a 0·3 per cent. solution, and 2½ grams per pint a 0·5 solution (circa). Anæsthesia may be induced and maintained in one of the two following ways: (1) The subject may be induced to the level of complete sensory loss with a single dose intravenous injection of 5 per cent. solution of pentothal; an intravenous saline drip containing 0·3 per cent. of pentothal is then set up and the rate of drip regulated to the anæsthetic requirements of the proposed surgical procedure. (2) An intravenous saline-pentothal drip containing 0·5 - 1 per cent. of pentothal is set up and the subject induced and maintained by regulating the rate of drip. Of these two methods, the first has been found the most convenient method in clinical practice. An indication of the rate of drip of these various solutions is that, in a standard transfusion set, 40 drops per minute is equivalent to about 140 c.c. per hour, or one pint in 4 hours.

When pentothal or evipan is given by continuous intravenous

of the clearance of pentothal from circulating blood by deviation and detoxication secures the rapid release of the respiratory centre from this level of anæsthetic depression.) Very shallow breathing accompanied by an appreciable fall of pulse pressure and large pupils which do not react to light on the other hand indicate that not only the respiratory centre but also the vasomotor centre is depressed by anæsthetic overdose. In this instance, a failing circulation hinders the clearance of pentothal from circulating blood; if anoxia is permitted to act, circulatory failure and subsequent syncope rapidly occurs. Hence the character of breathing and the radial pulse give clear and definite warning of impending overdose during the period which immediately follows the 30-second pause, and these signs may be checked by an examination of the pupils.

As the anæsthetist's experience of the anæsthetic and its administration increases, pentothal in his hands becomes a more flexible and a safer anæsthetic. (An experienced anæsthetist may safely produce deep anæsthesia, even to the level of depression of the respiratory centre, by single-dose intravenous injection of pentothal. This is possible only if ways and means of adequately oxygenating the subject are available for immediate use, for if an effective circulation is maintained and anoxia is avoided, anæsthetic depression is very rapidly reduced by the rapid clearance of pentothal from circulating blood. In the author's opinion, a small *single dose of pentothal, viz. 0 5 grams, injected* with appropriate speed, is a safer method of producing a given level of anæsthetic depression than the injection of a larger dose, viz. 1 gram, more slowly, for in clinical practice 0 5 grams of pentothal injected intravenously at a rapid rate produces deep anæsthesia for a short period of time, while 1 gram of pentothal injected more slowly may be made to produce a comparable level of anæsthetic depression which, however, is maintained for a longer period of time, and this is explained by the exponential nature of the excretion of pentothal from circulating blood.)

Continuous intravenous pentothal was extensively used during the 1939-1945 war as a maintenance anæsthetic for major surgical procedures, and was administered either in *repeated doses* or by *continuous intravenous administration* in a saline intravenous drip.

When repeated doses are used, anæsthesia to the level of

realised that such subjects were more susceptible than normal to these barbiturates injected intravenously at a proper rate. The most obvious result of surgical shock is a loss of tone of the whole cardiovascular system, with a diminished venous return and, in consequence, a diminished cardiac output: ignoring all else, this results in a diminished minute blood flow to each and every organ of the body. Consequently the clearance of pentothal or evipan from circulating blood by deviation to non-nervous tissues is slower than normal; moreover, the rate of detoxication of these barbiturates is reduced because of the diminution of the minute blood flow through the liver. The rate of clearance of evipan or pentothal from circulating blood is therefore slower in a case of surgical shock than in a normal subject; and in response to a given mass of evipan or pentothal injected intravenously at a proper rate the concentration of the anæsthetic in circulating blood, when accumulation has reached its maximum, is greater in a shocked subject than in a normal subject. Compared with a normal subject, the response of a shocked subject to a given mass of pentothal or evipan injected intravenously at a proper rate is, therefore, abnormally intense and prolonged, and this response can be attributed mainly to the diminished rate of clearance of these non-volatile anæsthetics from circulating blood produced by the diminished circulatory rate of the whole body. For example: the average dose of pentothal employed in 250 consecutive battle casualties in various degrees of surgical shock was 0·4 grams. Again, in an Army Command in the United Kingdom, seven deaths occurred in shocked subjects in a period of 20 months, following the intravenous injection of less than 0·8 grams of pentothal. In the Pearl Harbour action of 1941, it is said that deaths running into three figures followed the intravenous injection of pentothal in shocked battle casualties. This susceptibility to the action of intravenous evipan or pentothal is also observed in pathological conditions such as cardiac failure, and conditions such as myxœdema, when the metabolic rate and, in turn, the circulatory rate are reduced below normal limits.

When liver degeneration is present in experimental animals, Pratt and Cameron and de Saram have shown that a sub-lethal dose of reactive non-volatile barbiturates produced very deep and prolonged anæsthesia, or sometimes death of the subject. Such

administration, it is important to realize that the concentration of these barbiturates in the brain, in the blood and in the non-nervous tissues, reaches a state of equilibrium in about 30 minutes. *After about 20 minutes, therefore, the deviation of the barbiturate to non-nervous tissues is slow, and after 30 minutes it has, in effect, ceased.* The protective rôle of the deviation of these barbiturates to non-nervous tissues, therefore, reaches the limit of its usefulness about 20 - 30 minutes after intravenous administration commences; from this time onwards in the continuous administration of these anæsthetics, the rate of their clearance from the blood stream depends solely upon the rate of their detoxication. It follows that the clinical control of pentothal or evipan administered by continuous intravenous injection is less flexible and more hazardous than when they are administered intravenously in single dosage; but in spite of this, clinical experience has shown that the continuous intravenous administration of evipan or pentothal is a safe method of inducing and maintaining surgical anæsthesia in a normal subject when used by an experienced anæsthetist.)

The soundness of this conclusion, however, hinges on the qualifying phrase *in a normal subject.* When pathological conditions are present which render the excretion of evipan or pentothal sluggish and/or faulty, continuous intravenous administration is so dangerous a procedure as to condemn its use in clinical practice, while the intravenous administration of these barbiturates in single dosage requires great care and clinical acumen if overdose is to be avoided.

The normal rate of excretion of pentothal or evipan is diminished by any factor which reduces the rate of their clearance from circulating blood. Sluggish excretion is produced by pathological conditions which reduce the circulatory rate of the body, and sluggish and faulty detoxication occurs when certain pathological conditions of the liver are present.

During the years 1939-1945 there was ample opportunity to observe the response of subjects suffering from surgical shock to pentothal or evipan injected intravenously in single dosage. Most anæsthetists are familiar with the abnormally deep and prolonged anæsthesia, or even the death of the subject, following a small single dose of pentothal injected intravenously at a normal rate in subjects suffering from severe surgical shock. And it was quickly

amongst the malarias and dysenterics indicates, *in a very positive manner*, that the liver is the main source of the detoxication of pentothal in Man. It is significant that, as anæsthetic experience in Assam and Burma increased, the monthly reports of each medical unit indicated that anæsthetists independently tended to use dilute solutions of pentothal in hypnotic dosage and to abandon continuous intravenous pentothal anæsthesia in favour of inhalation anæsthesia for shocked and toxic battle casualties.

It is clear that the non-volatile narcotics now employed as intravenous anæsthetics, viz. evipan and pentothal, may be safely used in clinical anæsthetic practice for the induction and maintenance of surgical anæsthesia. Pentothal was effectively and safely employed during the late war for the induction and maintenance of anæsthesia for major surgical procedures, but it was the author's opinion then—and he still holds this opinion—that a greater measure of protection can be afforded the subject by anæsthetic maintenance with inhalation anæsthetics. (Whether evipan and pentothal are detoxicated by the liver or whether their detoxication is effected by the liver and other tissues, the fact remains that the anæsthetist has no control over the rate of their clearance from the blood stream; on this account, they are less safe than volatile anæsthetics whose absorption and excretion may be varied at will in upward and downward directions) It has been seen that certain pathological conditions may retard the rate of the clearance of these non-volatile intravenous anæsthetics from the blood stream; but their detoxication and excretion cannot be accelerated in any way. (*There is little doubt that the safety of these intravenous anæsthetics and the field of their clinical usefulness is determined mainly by the character of their excretion*) It can be concluded that the method of their administration, and the contra-indications to their use, has little in common with volatile blood-borne anæsthetics; and that their efficient, safe administration depends in a great measure on the clinical acumen and experience of the anæsthetist.

REFERENCES.

1. AUSCHUTZ Dent. Gesillschaft f. Chir. Berlin. April (1933).
2. CAMERON, G. R., and DE SARAM, G. S. W. (1939). *J. Path Bact.* 48, 59.
3. HARRIS, T. A. B., and McMARTIN, R. B. (1944). Unpublished.
4. MASSON, G., and BELAND, E. (1945) "Anesthesiology." 6, 483.

results are due to sluggish and faulty detoxication of the reactive non-volatile anæsthetic by the pathogenic liver. Consequently, the concentration of the anæsthetic in circulating blood, when accumulation has reached its maximum, is higher than that attained in a normal animal in response to sub-lethal dosage, and is maintained for a longer period of time. (Observations in experimental animals are not always applicable in Man; but in this instance an exact analogy can be drawn, for when liver inefficiency is present in Man, the intravenous injection of a single sub-lethal dose of evipan or pentothal produces abnormally deep and prolonged anæsthesia, and has resulted in the death of the subject.)

In temperate climates, liver inefficiency is *relatively uncommon.* It may occur with inflammation of the biliary tract and with any form of hepatitis Liver inefficiency may also be associated with the toxæmias, the fevers, acute or prolonged sepsis, the toxæmias of pregnancy, etc., and with the relative degrees of anoxia which often accompany the anæmias and cardiac failure. (In tropical climates, liver inefficiency is *relatively common*, and to the above causes must be added the liver inefficiency which may be associated with the acute stage of almost every common tropical disease, such as the dysenteries, the malarias, kala azar, etc., and with the secondary anæmias associated with the chronic stage of most tropical diseases. In all these pathological conditions liver inefficiency may occur with or without jaundice.)

During the years 1942-43, the incidence of malaria and dysentery amongst troops in Assam and Burma was very high, and these subjects were found to be particularly susceptible to small single dosage of pentothal administered intravenously. An associated liver inefficiency was suspected to be the cause of this susceptibility, and India Command made it possible for Captain R. B. McMartin, R.A.M C., to confirm by laboratory methods the association of liver inefficiency with the dysenteries and the malarias in these soldiers The author has records of six deaths, and more than a score of cases in which anæsthesia lasted from 5 - 22 hours after the intravenous injection of 0 5 grams of pentothal; there were, without doubt, other unreported cases of this nature in this area. The work of Masson and Beland (1945) on rats suggests that in these animals at least the liver is not essential to the efficient detoxication of pentothal; but experience

CHAPTER XVI

ORAL AND RECTAL ANÆSTHETICS

NON-IRRITATING anæsthetic liquids and soluble solids may be conveniently absorbed into circulating blood through the capillary bed of a hollow viscus such as the stomach or the rectum and sigmoid colon.

In clinical anæsthetic practice, all the anæsthetics in Table 41 have been used as pre-anæsthetic medicants by oral administration. Nowadays, those barbiturates of the first group of this Table which produce a standard response fairly slowly are most commonly employed as oral pre-anæsthetic medicants, and of these nembutal is perhaps the most popular in clinical anæsthetic practice.

When an anæsthetic is ingested orally, the mass of anæsthetic absorbed into circulating blood per unit time is determined by the mass of anæsthetic ingested, the rate of its diffusion through the mucosa into the stomach capillaries, its solubility in whole blood and the minute blood flow through the stomach capillaries. In resting conditions, the rate of absorption into circulating blood and, in turn, the rate and intensity of the response of the body to a given mass of anæsthetic ingested orally, are fairly uniform in a healthy subject if there is no emotional upset. Disease, and/or the emotional upset common before anæsthesia, may produce upward or downward variations in the minute blood flow through the stomach capillaries, and so cause significant variations in the character of gastric juice and in the rate of absorption of oral pre-anæsthetic medicants into circulating blood. In clinical practice, therefore, the rate and intensity of the body's response to oral pre-anæsthetic medicants may vary within wide limits; it is unwise, therefore, to exceed hypnotic dosage when the oral method of approach to circulating blood is employed in clinical anæsthetic practice.

Accurate timing of the period of maximum action of a pre-anæsthetic medicant is important, and variations in the rate of absorption of oral pre-anæsthetic medicants combine with delays,

5. Menegaux, G., and Scheiiage, L. (1934). *J. Chir. Paris* 44, 361.
6. Morton, L. G. (1942). *Aust. & N.Z. J. Surg.* 12, 119.
7. Pratt, T. W. (1933). *J. Pharmacol.* 48, 285.
8. Sollman, T. (1932) "A Manual of Pharmacology." 4th Ed. p. 740 W. B. Saunders & Co., London.
9. South African *Med. Journ.* Nov. 14th (1936). Report of Committee on "Deaths under Anæsthesia."

injected rectally in a $2\frac{1}{2}$ per cent. aqueous solution in dosage of 0·1 grams per kilo of body weight, paraldehyde in a 10 per cent. aqueous solution in dosage of one drachm per stone of body weight; evipan and pentothal are injected rectally mainly in children in a 3 per cent. aqueous solution in dosage of 45 milligrams per kilo of body weight—equivalent to one gram per 50 lb. dissolved in one ounce of water. This standard dosage produces basal anæsthesia in a healthy subject.

When introduced into the rectum in solution in water, these anæsthetics are rapidly absorbed from the solute through the mucosa into the rectal capillaries. This is a simple diffusion and solution process. The mass of anæsthetic, such as avertin, absorbed into circulating blood per unit time is determined by the volume of standard solution injected rectally, its diffusion rate through the mucosa into the capillaries of the part, its solubility in whole blood and the minute blood flow through the rectal capillaries. In a particular subject, the minute blood flow through the rectum in resting conditions can be held to be uniform, and it follows in clinical practice that *the mass of anæsthetic absorbed into circulating blood from the site varies as the volume of standard solution injected rectally.*

The character of absorption is exponential, and if a equals the volume of standard solution of avertin injected rectally, and $\frac{1}{b}$ equals the proportion of this avertin absorbed into the rectal capillaries per unit time at a resting metabolic rate, then in resting conditions, the progress of the absorption of avertin from the rectum into the blood of the portal circulation at each period of time can be represented thus:

$$\frac{a}{b} + \frac{a}{b}\left(1 - \frac{1}{b}\right) + \frac{a}{b}\left(1 - \frac{1}{b}\right)^2 + \frac{a}{b}\left(1 - \frac{1}{b}\right)^3$$

and so on.

Since an anæsthetic absorbed from the stomach or the rectum enters the blood of the portal circulation, it must pass through the liver before it can reach the systemic circulation. Passing from the portal venules of the liver to those of the hepatic vein, predominantly reactive anæsthetics such as avertin, paraldehyde, evipan and pentothal are, therefore, subjected to the detoxicating action of the cells of the liver in a manner similar to that of metabolites absorbed from the bowel. In consequence of this, the

unavoidable in busy hospital practice, to make this accurate timing a difficult problem.

If anæsthetics with a slow excretory rate and a consequent prolonged action are administered orally 1½ hours before the anticipated time of anæsthetic induction, it is found that fairly accurate timing can be achieved. For this reason, the non-volatile anæsthetics of the first group of Table 41, whose rate of excretion is slow, are most suitable for use as oral pre-anæsthetic medicants; the remaining members of this Table are more suitable for some other method of approach to circulating blood.

When the rate of absorption is abnormally slow, the delayed response of the members of the *first* sub-group makes for inaccurate timing; when the rate of absorption is abnormally rapid, inaccurate timing occurs with the members of the *third* sub-group, for the response of the body to their action is fairly rapid. The response of the body to the members of the *second* sub-group is fairly slow, and since the rate of their excretion is slow they represent the best compromise for oral administration.

Nowadays, nembutal and sodium soneryl are most commonly used orally as pre-anæsthetic medicants. They are used mainly in children to produce a state ranging from amnesia to deep hypnosis, prior to anæsthetic induction, and they are administered in single dosage by mouth in doses of 0 5 grains of the barbiturate per stone of body weight, 1½ hours before anæsthetic induction

The minute blood flow through the rectum and sigmoid colon is not subject to such wide fluctuations, and the rate of absorption of anæsthetics from this site and the response of the subject to standard rectal dosage are more uniform than when the same anæsthetic is administered orally. For this reason, a deeper level of anæsthetic depression can be more safely produced when anæsthetics are administered rectally than when the same anæsthetic is given by mouth. Rectal anæsthetics are employed in clinical practice to produce basal anæsthesia, that is, anæsthesia to the level of the complete depression of the higher centres of the brain.

In the past, many anæsthetics have been used in clinical practice by rectal injection. Nowadays avertin, paraldehyde and the very rapidly acting barbiturates, evipan and pentothal, are the only anæsthetics commonly employed for this method of approach to circulating blood, and they are used in basal doses. Avertin is

injected rectally in a 2½ per cent. aqueous solution in dosage of 0·1 grams per kilo of body weight, paraldehyde in a 10 per cent. aqueous solution in dosage of one drachm per stone of body weight; evipan and pentothal are injected rectally mainly in children in a 3 per cent. aqueous solution in dosage of 45 milligrams per kilo of body weight—equivalent to one gram per 50 lb. dissolved in one ounce of water. This standard dosage produces basal anæsthesia in a healthy subject.

When introduced into the rectum in solution in water, these anæsthetics are rapidly absorbed from the solute through the mucosa into the rectal capillaries. This is a simple diffusion and solution process. The mass of anæsthetic, such as avertin, absorbed into circulating blood per unit time is determined by the volume of standard solution injected rectally, its diffusion rate through the mucosa into the capillaries of the part, its solubility in whole blood and the minute blood flow through the rectal capillaries. In a particular subject, the minute blood flow through the rectum in resting conditions can be held to be uniform, and it follows in clinical practice that *the mass of anæsthetic absorbed into circulating blood from the site varies as the volume of standard solution injected rectally.*

The character of absorption is exponential, and if a equals the volume of standard solution of avertin injected rectally, and $\frac{1}{b}$ equals the proportion of this avertin absorbed into the rectal capillaries per unit time at a resting metabolic rate, then in resting conditions, the progress of the absorption of avertin from the rectum into the blood of the portal circulation at each period of time can be represented thus:

$$\frac{a}{b} + \frac{a}{b}\left(1 - \frac{1}{b}\right) + \frac{a}{b}\left(1 - \frac{1}{b}\right)^2 + \frac{a}{b}\left(1 - \frac{1}{b}\right)^3$$

and so on.

Since an anæsthetic absorbed from the stomach or the rectum enters the blood of the portal circulation, it must pass through the liver before it can reach the systemic circulation. Passing from the portal venules of the liver to those of the hepatic vein, predominantly reactive anæsthetics such as avertin, paraldehyde. evipan and pentothal are, therefore, subjected to the detoxicating action of the cells of the liver in a manner similar to that of metabolites absorbed from the bowel. In consequence of this, the

concentration of the anæsthetic entering the systemic circulation when absorbed from a hollow viscus, is less than its concentration in the portal circulation. Detoxication of reactive anæsthetics by the liver is exponential in character. If a proportion, $\frac{1}{c}$ of the mass of a reactive anæsthetic such as avertin is detoxicated per unit time, then the mass of anæsthetic entering the systemic circulation at each successive period of time, in response to a volume of avertin injected rectally, is as follows:

During the first period of time, after the rectal injection of a volume a of a standard solution of avertin, $\frac{a}{b}$ is absorbed into the portal circulation and is carried to the liver. Of this, $\frac{a}{bc}$ is detoxicated in the liver, and the remainder, $\left(\frac{a}{b} - \frac{a}{bc}\right)$ or $\frac{a}{b}\left(1-\frac{1}{c}\right)$ enters the systemic circulation. During the second period of time, $\frac{a}{b}\left(1-\frac{1}{b}\right)$ is absorbed from the rectum into the portal circulation, and of this $\frac{a}{bc}\left(1-\frac{1}{b}\right)$ is detoxicated by the liver and the remainder, $\frac{a}{b}\left(1-\frac{1}{b}\right) - \frac{a}{bc}\left(1-\frac{1}{b}\right)$ or $\frac{a}{b}\left(1-\frac{1}{c}\right)\left(1-\frac{1}{b}\right)$ enters the systemic circulation. During the third period of time $\frac{a}{b}\left(1-\frac{1}{c}\right)\left(1-\frac{1}{b}\right)^2$ enters the systemic circulation, and so on. The absorption of a reactive anæsthetic such as avertin, into systemic blood from the capillary bed of a hollow viscus such as the rectum, is thus exponential in character; and in response to single dosage, the greatest mass of anæsthetic enters the systemic circulation during the first period of time, and the mass absorbed gradually decreases and in a logarithmic manner as absorption proceeds. The progress of absorption into the systemic circulation may be represented:

$$\frac{a}{b}\left(1-\frac{1}{c}\right) + \frac{a}{b}\left(1-\frac{1}{c}\right)\left(1-\frac{1}{b}\right) + \frac{a}{b}\left(1-\frac{1}{c}\right)\left(1-\frac{1}{b}\right)^2$$

and so on.

This simplified description of the absorption of a reactive non-volatile anæsthetic into systemic blood from the capillary bed of a hollow viscus such as the stomach or rectum serves to emphasise not only the factors which influence the rate of its absorption into systemic blood, but also the fact that the anæsthetic reaches the systemic circulation via the portal circulation. Because reactive anæsthetics absorbed from a hollow viscus are subjected to the detoxicating action of the liver before they enter systemic blood there is a material difference between the rectal

and the intravenous dose of a given reactive anæsthetic. For example, the recommended rectal dose of pentothal for the production of basal anæsthesia in a 150-lb. man is in the region of 3 grams, while the maximal intravenous dose required to produce a comparable level of anæsthetic depression is considerably less than 1 gram. This is in keeping with the minute blood flow through the liver in resting conditions, for the portal blood flow of 322 c.c. per minute is almost thrice the minute volume of arterial blood flow through the liver, viz. 137 c.c.

The clearance of reactive rectal anæsthetics from systemic blood is exponential in character and depends upon the deviation of these anæsthetics to non-nervous tissues and their detoxication by the liver. Both deviation and detoxication are rapid in a healthy subject, and the rate of their uptake and clearance from systemic blood is such that an effective concentration is reached in systemic blood—in the case of avertin it is 6 - 9 milligrams per cent.—about 20 to 30 minutes after the injection of standard rectal dosage. This represents the level of maximal accumulation of the anæsthetic in systemic blood when the rate of uptake equals the rate of clearance; in clinical practice, a concentration of 6 - 9 milligrams of avertin per cent. in systemic blood produces anæsthesia to the level of the complete depression of the higher centres of the brain—basal anæsthesia—in a healthy subject.

There are a number of factors which pre-dispose to the irregular response of the body to standard dosage when rectal anæsthetics are employed. An increased metabolic rate, such as occurs in a toxic goitre, leads to an increased rate of absorption from the hollow viscus, but this is compensated for by rapid detoxication, and the net result is *a more rapid response and a shorter period of action* Overdose may inadvertently occur in obese subjects or in subjects with a large tumour such as an ovarian cyst, unless the actual body weight is re-assessed with regard to the weight of inactive adipose tissue or the tumour. When inflammatory conditions of the rectum and/or the colon are present, the response of the body to standard rectal dosage may be rapid and intense because of rapid absorption from the hollow viscus; and when such rapid absorption is combined with liver inefficiency, such as in amœbiasis, the response of the body to standard rectal dosage is rapid, and overdose may readily

occur, for the rate of clearance of the anæsthetic from circulating blood is sluggish and faulty. The rate of clearance of these *predominantly reactive rectal anæsthetics is sluggish* when pathological conditions reduce the circulatory rate, and sluggish and faulty detoxication occurs when liver inefficiency is present. It must be emphasised that the efficient detoxication of rectal anæsthetics is essential to safe use in clinical anæsthetic practice, for the response to standard rectal dosage based on the subject's body weight depends not only upon the detoxication of the reactive *anæsthetic from portal blood, but also upon the clearance* of the reactive anæsthetic from systemic blood. Since the rate of detoxication of predominantly reactive anæsthetics cannot be wittingly influenced by the anæsthetist, and because the rate and efficiency of detoxication may be significantly reduced by disease, it is clear that rectal anæsthesia is unsuitable for use in certain subjects and that the safety of the administration of rectal anæsthetics in suitable subjects depends alone upon the control of their absorption into the blood stream from the hollow viscus.

In suitable subjects, the method of administration of rectal anæsthetics is planned to permit the particular subject's response during absorption to furnish an accurate index of his susceptibility to the anæsthetic employed With this end in view, Shipway introduced a method of using avertin which has since been known as " divided dosage "; it may be described as follows:

A standard of 2½ per cent. solution of avertin, 0·1 grams per kilo of body weight, is prepared and tested with congo red; this volume of avertin is looked upon as the maximum dose which is not in any circumstances to be exceeded. Three-quarters of this volume is run into the rectum through a fine rubber catheter as rapidly as possible without producing expulsion from the viscus; the catheter is clipped and left *in situ* Thirty minutes later, the subject's response to this dose of avertin is observed. If anæsthesia is too deep, an appropriate amount of the fluid content of the rectum is withdrawn. If anæsthesia is too light, part or all the remaining quarter of the pre-determined dose is injected rectally in keeping with the observed response of the subject. At the end of an additional fifteen minutes (forty-five minutes after the administration began) the subject should have attained a satisfactory state of basal anæsthesia. A modification of this technique

—in the present writer's opinion, offering an even better opportunity to suit the dose to the particular subject—is also used in clinical practice:

The pre-determined maximum dose of avertin is prepared as before, and the solution run into the rectum slowly, at a rate which would dispose of three-quarters of the maximum dose in about ten minutes. When consciousness is lost, irrespective of the volume administered, the catheter is clipped and left *in situ*. If, however, consciousness has not been lost when three-quarters of the maximum dose has been injected into the rectum, the catheter is clipped and left *in situ*. Thirty minutes after the commencement of rectal injection, the subject's response is observed and, as before, the rectal content is withdrawn or added to, in accord with the subject's response. Forty-five minutes after the commencement of rectal injection, basal anæsthesia should be complete.

The principle of divided dosage should be employed in the administration of all rectal anæsthetics, for it confers the greatest measure of safety

CHAPTER XVII

SUBCUTANEOUS AND INTRAMUSCULAR ANÆSTHETICS

NON-IRRITATING, non-volatile blood-borne anæsthetics may be administered in single hypnotic dosage by subcutaneous or intramuscular injection. This method of approach to systemic blood is employed when a rapid response of the body to the anæsthetic is not required and when hypnosis is the deepest level of anæsthetic depression desired. It is an advantage to use those anæsthetics whose rate of excretion is slow and whose duration of action is consequently prolonged; and generally speaking, all the non-irritants of the first group of anæsthetics shown in Table 41, whose rate of excretion is very slow, may be used in this fashion as pre-anæsthetic medicants. In clinical practice, however, morphia and its derivatives and/or scopolamine are most commonly employed by subcutaneous or intramuscular injection, for they provide the best compromise between the rate of response and the duration of action required in a pre-anæsthetic medicant.

Injected in aqueous solution into a subcutaneous or an intramuscular site, anæsthetic solids such as morphia pass by diffusion to the capillaries of the part and are dissolved in systemic blood. The mass of anæsthetic entering the systemic circulation per unit time from a subcutaneous or an intramuscular site is determined by the mass of anæsthetic injected, by the rate of diffusion from the site of its injection into the capillaries of the part, by its solubility in whole blood and by the volume of blood flow through the capillaries of the part per unit time. The character of the absorption of a non-volatile anæsthetic, such as morphia, from a subcutaneous or intramuscular site into systemic blood may be described as follows:

If a equals the mass of anæsthetic injected, and $\frac{1}{b}$ equals the proportion of this mass which is absorbed into circulating blood from the site of injection per unit time at a resting rate, then the progress of absorption can be represented:

$$\frac{a}{b} + \frac{a}{b}\left(1 - \frac{1}{b}\right) + \frac{a}{b}\left(1 - \frac{1}{b}\right)^2 + \frac{a}{b}\left(1 - \frac{1}{b}\right)^3 \text{ and so on.}$$

The absorption of non-volatile anæsthetics from a subcutaneous or an intramuscular site is thus exponential in character; the greatest mass of anæsthetic enters the systemic circulation during the first period of time after injection, and the mass absorbed gradually decreases in a logarithmic manner as absorption proceeds.

Meanwhile, the excretion of anæsthetic solids such as morphia from the body proceeds at a relatively slow rate, and the concentration of the anæsthetic in systemic blood continues to rise until, at length, the rate of its clearance equals the rate of its absorption from the site of injection into systemic blood. At this point, the concentration of the anæsthetic in systemic blood has reached its maximum value and anæsthetic depression its greatest intensity, and from this time onwards, the rate of excretion gradually overtakes the rate of absorption, and anæsthetic recovery slowly proceeds as the concentration of the anæsthetic in systemic blood gradually falls.

In clinical practice, 0·2 milligrams of morphia per kilo of body weight and 0·02 milligrams of the more potent scopolamine, are used for subcutaneous or intramuscular injection in single dosage as a pre-anæsthetic medicant. In a normal subject, this dosage produces a state of light hypnosis when maximum concentration has been achieved in systemic blood. In the case of morphia, this occurs within twenty to thirty minutes of injection and lasts for about one to four hours The maximal action is produced more slowly in the case of scopolamine, and hypnosis occurs in forty-five to sixty minutes and lasts for about two to six hours. In normal subjects, consistent and reliable results are obtained when these members of the third sub-group of anæsthetics shown in Table 41 are used in the above single dosage as pre-anæsthetic medicants by subcutaneous or intramuscular injection.

The rate of absorption into systemic blood from a subcutaneous or an intramuscular site varies as the minute blood flow through the site. When the metabolic rate and in turn the circulatory rate are raised, as in exophthalmic goitre, the fevers, etc., the absorption of the anæsthetic is more rapid than normal; in myxœdema, surgical shock, cardiac failure, etc , in which the circulatory rate is lowered, absorption from a subcutaneous or an intramuscular site is slower than normal. The influence of a sluggish circulatory rate on the absorption of a non-volatile anæsthetic from a sub-

cutaneous or an intramuscular site may be exemplified in the response to subcutaneous morphia in a subject suffering from the severe surgical shock which was so common during the period 1939-1945.

Most anæsthetists are familiar with the shocked blitz or battle casualty admitted for treatment some hours after injury, who had received up to three-quarters grain of morphia within perhaps two hours. Because of his shocked condition, the minute blood flow through the site of injection and, in turn, the rate of absorption of morphia into the blood stream, were sluggish, and it was common to be struck by the meagre response of the subject to the total amount of morphia injected. But as the cardiovascular system recovered with efficient resuscitation, the minute blood flow through the site of injection increased and the clinical signs of morphia overdose rapidly appeared, with shallow breathing and pin-point pupils.

Variations in the absorption rate of anæsthetics injected subcutaneously or intramuscularly in single hypnotic dosage may result in inaccurate timing of the period of their maximum action, but such variations are not a source of danger to the subject. If, however, the excretion of these anæsthetics is sluggish and/or faulty, the response of the subject to standard dosage may be abnormally intense and prolonged. This, too, is of little consequence when single hypnotic dosage is employed for premedication, and such a response may be the anæsthetist's first warning of the inability of the subject to detoxicate at a normal rate the intravenous barbiturate which is to follow. When liver inefficiency is present, repeated cutaneous or intramuscular injections of morphia in hypnotic dosage may result in accumulation with consequent overdose. The author has records of an adult male who died from anoxia in the coma which followed the fifth successive injection of morphia ¼ grain given six-hourly; at autopsy, extensive active amœbias of the liver was found to be present. Scopolamine is probably a safer pre-anæsthetic medicant than morphia when liver inefficiency is present, for about 33 per cent. of the injected dose is excreted by the kidneys Morphia proves to be a safer pre-anæsthetic medicant when renal inefficiency is present, for only about 10 per cent. of the injected morphia is excreted by the kidneys. Codein and heroin are seldom used as pre-anæsthetic medicants, since they are predominantly non-reactive in character.

CHAPTER XVIII

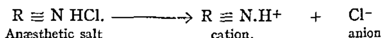
LOCAL ANÆSTHETICS

THE local anæsthetics in common clinical use are reactive, non-irritant narcotics of high molecular weight and potency whose detoxication products neither cumulate nor are harmful. Local anæsthetics are not suitable for use as blood-borne anæsthetics, and they are applied directly to mucous membranes, etc., or are injected with syringe and needle with anatomical accuracy into the vicinity of the peripheral nerve or group of nerves which it is proposed to subject to their action. They differ from blood-borne anæsthetics in their method of approach to the site of their drug fixation, but, having been concentrated at the surface of neurones, their uptake is similar to that of other narcotics of comparable physical properties, and their fixation and the subsequent biological response elicited are identical with those of other narcotics.

Since the mechanism of drug fixation of local anæsthetics is identical with that of blood-borne anæsthetics, it is not surprising to find, when a local method of approach is adopted for narcotics which are employed as blood-borne anæsthetics, that these narcotics produce local anæsthesia. Gros (1910) found, when chloroform, amylene hydrate, paraldehyde, ethyl urethane, etc., were injected intracutaneously in man, that local anæsthesia with hyperæsthesia at the margin of the wheal was produced, and that these same blood-borne anæsthetics, when applied directly to a frog's sciatic nerve, abolished the ability of the nerve to conduct impulses. Again, the addition of a blood-borne anæsthetic to a local anæsthetic solution potentiates its action. Kockmann and Hurtz (1923) observed that the addition of morphine to a solution of cocaine increased the ability of the solution to " block " motor nerves, and this is an example of the additive effect of anæsthetic mixtures fixed by the same receptors. Gros found that the concentration of a blood-borne anæsthetic necessary to depress the functional activity of peripheral nerves was about six times that required to depress the cells of the central nervous system.

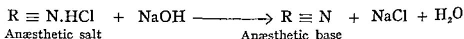
All the important local anæsthetics in common clinical use are the salts of primary, secondary or tertiary amines. Of the twenty-six local anæsthetics cited by Hewer in " Recent Advances in Anæsthesia and Analgesia " (1944), nineteen are hydrochlorides of the anæsthetic base. These salts are freely soluble in water, and are neutral or slightly acid in reaction.

In solution, the anæsthetic salt, is ionized to form the ions, $R \equiv N.H^+$ and Cl^-, but the degree of ionization which occurs in the case of weak bases such as cocaine, procaine, etc., is very small.

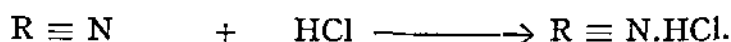


$$\underset{\text{Anæsthetic salt}}{R \equiv N\,HCl.} \longrightarrow \underset{\text{cation.}}{R \equiv N.H^+} + \underset{\text{anion}}{Cl^-}$$

When, however, these salts are brought into contact with an alkali, free anæsthetic base is liberated. This chemical reaction is freely reversible, and use is made of this fact in the preparation of 1-1500 Nupercaine solution, for 5 minims of dilute hydrochloric acid are added to each litre of this preparation (and are responsible for the crystal clearness of the solution).



$$\underset{\text{Anæsthetic salt}}{R \equiv N.HCl} + NaOH \longrightarrow \underset{\text{Anæsthetic base}}{R \equiv N} + NaCl + H_2O$$



$$R \equiv N + HCl \longrightarrow R \equiv N.HCl.$$

This separation of free anæsthetic base is one of the most important reactions occurring when local anæsthetics are used in clinical practice, for tissue cells and tissue fluids are normally alkaline in reaction Consequently, free anæsthetic base is liberated in amounts that depend upon the alkalinity of the tissues at the site of injection. Overton has shown that the free bases of alkaloids are more active pharmacologically than their corresponding salts, and that the free anæsthetic bases are four to eight times more potent than their corresponding anæsthetic salts.

When the dissociation of free anæsthetic base is such that a slight opalescence occurs in the injected solution, positively charged ions of free base in suspension are strongly absorbed by negatively charged peripheral nerve fibres and nerve endings. When, however, the tissues are abnormally alkaline, the separation of free anæsthetic base is excessive, and free base is aggregated into particles sufficiently large to cause their precipitation from

solution. In this instance, the anæsthetic effectiveness of the solution is diminished: on the one hand in keeping with the reduction of surface area which occurs by reason of the size of the precipitated particles, and on the other in keeping with the reduction of the concentration of the injected solution which occurs by reason of the amount of base precipitated from solution. In spinal anæsthesia, for example, when cerebrospinal fluid is more alkaline than normal, cloudiness is seen in the syringe after the aspiration of C.S.F., prior to the intrathecal injection of the solution; and in such subjects spinal anæsthesia is often unsatisfactory or fails completely. Since this separation of free anæsthetic base is in the nature of a titration, it follows, when the available alkali has combined, that no further separation of free base occurs from this cause, and the intrathecal injection of sufficient additional local anæsthetic to produce an effective concentration should result in a normal response. In such a case the writer observed that the injection of additional local anæsthetic was, in fact, followed by normal spinal anæsthesia. Sollmann (1918) has confirmed these observations of Gros, and there is little doubt that a strongly alkalinised local anæsthetic solution is not effective.

Gerlough (1931) and others have studied the effect of an increased acidity of local anæsthetic solutions. He observed at a pH of 5-6, that the anæsthetic potency of a solution of butyn was greatly reduced—a result due, without doubt, to a lack of free, potent anæsthetic base in solution. The pus of an acute abscess has a pH of 5-6 (circa), and this is one reason for the frequent failure of local anæsthetics injected into an inflammatory site.

Gros (1910) observed that the anæsthetic activity of cocaine, procaine, alypine, stovaine and beta eucaine varied as the oil/water partition coefficient of their anæsthetic bases. Adams *et al.* (1926) and Vleit and Adams (1926) found that the anæsthetic activity of local anæsthetics varied as their ability to lower the surface tension of water, and Evans and Benedict (1930) reported a close parallel between the anæsthetic activity of local anæsthetics and ability to lower the oil/water interface tension. They are of the opinion that ability to lower the oil/water interface tension is the most accurate index of anæsthetic potency—which is what might be expected of drugs high in molecular weight and effective

in dilute solution. These factors, however, are all physical properties which favour the escape tendency of local anæsthetics from extracellular fluid to tissue cells.

The free anæsthetic base is very soluble in lipoid, and insofar as the uptake of a drug influences its fixation, this lipoid solubility is responsible for the anæsthetic potency of the free base relative to its salt, for its uptake by peripheral nerves, which contain 20 per cent. (circa) of lipoid, is rapid and facile. Any factor such as excessive acidity or excessive alkalinity, preventing the accumulation of an effective concentration of free anæsthetic base in solution in extracellular fluid, diminishes the anæsthetic effectiveness of the local anæsthetic solution injected; for, while the water solubility of the salt allows its ready concentration in extracellular fluid, it is the high lipoid solubility of the free base which favours its uptake and subsequent fixation by the cell.

The uptake and, in turn, the concentration-action relation of local anæsthetics, are exponential in character; and the response of cells and enzymes to local anæsthetics is a *graded* response and is proportional to the logarithm of the concentration of the local anæsthetic in the extracellular fluid which surrounds the cells. The paralysis of the conductivity of peripheral nerves by local anæsthetics, however, is a typical *all-or-none* response, and the character of this response is determined by the nature of the passage of nerve impulses in nerve fibres

Nerve fibres possess the property of excitability and conductivity. The excitability of a nerve fibre varies in health and disease, and there is a certain threshold of stimulus which must be applied to a nerve fibre before a response can be elicited. When the stimulus exceeds this certain minimum intensity, it produces a *change* at the spot stimulated, the presence of which produces a similar change in adjacent areas of the nerve fibre, and a wave of change—a nerve impulse—travels along the fibre. Except in certain antidromic fibres, such as the vaso-dilators of the posterior spinal nerve roots, nerve impulses travel only in one direction. Healthy nerve tissue reacts vigorously when a wave of change, a nerve impulse reaches it, provided that the stimulus applied to the nerve fibre is above the threshold strength and the fibre is healthy, the intensity of the impulse produced is independent of the strength of the exciting stimulus, and the nerve impulse in the fibre is

always of maximum intensity. In a nerve trunk, the stronger the stimulus, the greater the number of individual fibres of the trunk which respond, and when the stimulus is sufficient to excite all the fibres of the trunk, an increase of the stimulus above this value produces no further increase in the intensity of the nerve impulse in the nerve trunk.

If a nerve trunk is subjected to the action of an effective concentration of a narcotic, its excitability and the rate of conduction are both reduced and the intensity of the nervous impulse in the trunk is diminished in a graded manner in keeping with the degree of narcosis. When a nerve impulse, travelling along this nerve trunk, enters the narcotised zone, the intensity of the impulse is immediately diminished in keeping with the degree of narcosis. Kato (1924) observed that no further decrease in the intensity of the impulse occurred in its passage through the narcotised zone. *This is called conduction without decrement.* He observed, moreover, that when this impulse reached normal tissue again, its strength was then increased to its original intensity. It follows that a nerve block produced by local anæsthetics, to be effective, must be absolute, and the narcotised zone must reduce the intensity of the nerve impulse in all the fibres of the nerve below the minimum threshold strength necessary to stimulate healthy fibres. Unless this is done, the nerve impulse in each fibre of the trunk, however feeble it may have become in its passage through the narcotised zone, will, on reaching normal nervous tissue, be restored again to its original intensity, and the strength of the impulse in the trunk will, in turn, be restored to its original strength

Hence, although peripheral nerves are depressed in a graded manner by local anæsthetics, the intensity of anæsthetic depression must attain a certain minimum threshold value if the passage of nerve impulses in a nerve is to be *blocked* and the paralysis of the conductivity of a peripheral nerve by local anæsthetics is, therefore, a typical *all-or-none* reaction.

It follows that there is a certain minimum threshold concentration below which a given local anæsthetic fails to block the passage of nerve impulses in peripheral nerves, and this minimum threshold concentration varies for a given local anæsthetic in respect to different types of peripheral nerve fibres. When an effective con-

centration of a local anæsthetic was injected intracutaneously, Rohde (1921) observed that light touch was first abolished and then, in order, the perception of heat and cold, pain, touch, and finally deep pressure. Motor fibres require a greater concentration of a given local anæsthetic to depress them than sensory fibres When an effective concentration of a local anæsthetic is injected into the vicinity of a mixed nerve, the individual susceptibility of the various fibres ensure that the afferent fibres which carry impulses of light touch from the skin are first blocked and then, in order, those responsible for temperature sense, pain, touch and deep pressure Recovery from the effect of local anæsthesia occurs in the reverse order, and a certain amount of hyperæsthesia appears before normal function is finally established.

Occasionally in clinical practice subjects are encountered who fail to respond in a characteristic fashion to an effective concentration of a local anæsthetic injected with anatomical accuracy Such subjects have been termed " rachi-resistant " subjects. This term is frequently employed in current anæsthetic literature with the implication that it is the result of a personal and peculiar non-uniformity—an idiosyncrasy of the subject in his relation to local anæsthetics This is seldom the case, and rachi-resistance can usually be attributed to factors such as the excessive acidity of inflammatory tissue, hindering the uptake of an effective concentration of the anæsthetic by the cell, or to factors producing a rapid dilution or dissociation of the local anæsthetic at the site of injection.

The concentration of the injected solution of local anæsthetic may be reduced below the necessary threshold concentration by excessive dilution with tissue fluid as, for example, when excessive barbotage is employed in spinal anæsthesia. It may be diluted by the excessive precipitation of free anæsthetic base caused by the abnormal alkalinity of the tissues, and it will always be progressively reduced by the absorption of the anæsthetic from the site of injection into circulating blood.

The mass of a given local anæsthetic absorbed into circulating blood per unit time from a given extra-vascular site of injection depends on the mass injected and on the volume of blood flow through this site per unit time For example, if a equals the mass

of local anæsthetic injected, and $\frac{1}{b}$ equals the constant fraction of this mass absorbed into circulating blood per unit time from this site, then:
In the first period $\frac{a}{b}$ is absorbed and $a\left(1-\frac{1}{b}\right)$ remains at the site.
In the second period, $\frac{a}{b}\left(1-\frac{1}{b}\right)$ is absorbed and $a\left(1-\frac{1}{b}\right)^2$ remains.
In the third period, $\frac{a}{b}\left(1-\frac{1}{b}\right)^2$ is absorbed and $a\left(1-\frac{1}{b}\right)^3$ remains at the site of injection, and so on.

Owing to the absorption of local anæsthetic in circulating blood, the concentration of the local anæsthetic at the site of injection therefore decreases in a logarithmic manner and falls with each successive period of time from a to $a\left(1-\frac{1}{b}\right)$ to $a\left(1-\frac{1}{b}\right)^2$ to $a\left(1-\frac{1}{b}\right)^3$ and so on. It falls below the minimal threshold concentration necessary to depress the conductivity of the peripheral nerves with which it is in contact in a period of time which depends on the mass injected, on the minute blood flow through the particular site of injection and on the physical properties of the local anæsthetic. The duration of anæsthesia, therefore, depends upon the mass injected, the nature of the site of injection and the physical properties of the particular local anæsthetic; there may also be other factors.

The rate of absorption of a local anæsthetic from a given site of injection may be delayed, and the duration of anæsthesia correspondingly increased, by the vaso-constriction produced by 5 minims of adrenaline hydrochloride, 1-1000, added to each 50 c.c. of the local anæsthetic solution employed; but, irrespective of the volume of local anæsthetic solution used for any given anæsthetic preparation, it is unwise to use more than 15 minims of 1 - 1000 adrenaline in a 1 - 200,000 dilution for this purpose. In sites containing erectile tissue, such as the corpora cavernosa, the use of adrenaline to delay absorption is open to criticism, for gangrene has been reported following its use in local anæsthesia in this situation. In sympathetico-tonic subjects and in subjects with cardiac disease, the use of adrenaline in local anæsthetic solution is not without risk, and when chloroform is to be used as an adjuvant to local anæsthesia, the presence of adrenaline in the injected solution is gravely dangerous because of the possibility of a ventricular fibrillation. When the nature of the site permits the application of a tourniquet prevents, or reduces to infinitesimal

centration of a local anæsthetic was injected intracutaneously, Rohde (1921) observed that light touch was first abolished and then, in order, the perception of heat and cold, pain, touch, and finally deep pressure. Motor fibres require a greater concentration of a given local anæsthetic to depress them than sensory fibres When an effective concentration of a local anæsthetic is injected into the vicinity of a mixed nerve, the individual susceptibility of the various fibres ensure that the afferent fibres which carry impulses of light touch from the skin are first blocked and then, in order, those responsible for temperature sense, pain, touch and deep pressure. Recovery from the effect of local anæsthesia occurs in the reverse order, and a certain amount of hyperæsthesia appears before normal function is finally established.

Occasionally in clinical practice subjects are encountered who fail to respond in a characteristic fashion to an effective concentration of a local anæsthetic injected with anatomical accuracy. Such subjects have been termed " rachi-resistant " subjects. This term is frequently employed in current anæsthetic literature with the implication that it is the result of a personal and peculiar non-uniformity—an idiosyncrasy of the subject in his relation to local anæsthetics. This is seldom the case, and rachi-resistance can usually be attributed to factors such as the excessive acidity of inflammatory tissue, hindering the uptake of an effective concentration of the anæsthetic by the cell, or to factors producing a rapid dilution or dissociation of the local anæsthetic at the site of injection.

The concentration of the injected solution of local anæsthetic may be reduced below the necessary threshold concentration by excessive dilution with tissue fluid as, for example, when excessive barbotage is employed in spinal anæsthesia. It may be diluted by the excessive precipitation of free anæsthetic base caused by the abnormal alkalinity of the tissues, and it will always be progressively reduced by the absorption of the anæsthetic from the site of injection into circulating blood.

The mass of a given local anæsthetic absorbed into circulating blood per unit time from a given extra-vascular site of injection depends on the mass injected and on the volume of blood flow through this site per unit time. For example, if a equals the mass

maximum cumulation has occurred, may well be an effective concentration for the cells of the central nervous system. In this instance, as the concentration of the local anæsthetic in circulating blood increases, the following sequence of events occurs. Amnesia and a state of happy inebriation are first observed, and are followed by anxiety, vertigo, dyspnœa and extreme pallor with perhaps a cold sweat. Loss of consciousness with all the signs of cardio-vascular collapse then occur, with perhaps a brief convulsion, then Cheyne Stokes breathing, respiratory arrest and death within a few minutes from secondary cardiac failure. These clinical signs indicate that the sequence of absorption of local anæsthetic by the brain is similar to that of ethyl alcohol. They are the manifestations of a toxic concentration of the local anæsthetic in circulating blood, and in clinical practice it has been observed that *if death has not occurred within the first few minutes of their onset, ultimate recovery will, in the absence of other factors, invariably occur.* This clinical observation is in accord with the exponential nature of the absorption of local anæsthetics into, and their excretion from, circulating blood; for, if death has not occurred when accumulation has reached its maximum, and if the depressing effect of anoxia is avoided and the circulation is supported by the prompt institution of artificial respiration with an oxygen atmosphere, recovery should occur. On the one hand, the mass of local anæsthetic entering circulating blood decreases in a logarithmic manner, and on the other, detoxication of the drug by the liver continues so long as a circulation persists; it follows that the concentration in circulating blood and consequently in the brain must diminish. It is clear that artificial respiration with an oxygen atmosphere in the Trendelenburg position not only supports the circulation, but also eliminates the danger of anoxia. *This manœuvre holds an indispensible place in the treatment of toxic symptoms during local anæsthesia, for it is the only means at our disposal which results in the continued elimination of local anæsthetics from circulating blood.* It is to be emphasised that analeptic drugs do nothing to reduce the concentration of local anæsthetics in circulating blood. They are cardiovascular stimulants, and as such may with value be employed as adjuvants to the above treatment.

The smallest mass of a local anæsthetic injected intravenously

proportions, the absorption of local anæsthetics from the site of injection and is the means of increasing the duration of anæsthesia.

The mass of local anæsthetic absorbed into circulating blood from an extravascular site of injection can be represented thus:

$$\frac{a}{b} + \frac{a}{b}\left(1 - \frac{1}{b}\right) + \frac{a}{b}\left(1 - \frac{1}{b}\right)^2 + \frac{a}{b}\left(1 - \frac{1}{b}\right)^3$$

and so on.

Absorption into circulating blood is exponential in character; the greatest mass of local anæsthetic is absorbed in the first period of time and the mass absorbed decreases in a logarithmic manner as absorption proceeds.

The distribution of local anæsthetics absorbed into circulating blood is the same as that of all other non-volatile anæsthetics. A proportion is absorbed and fixed by nervous tissue cells; a proportion is deviated by its absorption and fixation by non-nervous tissues; a proportion may be eliminated by the kidneys, and a proportion is detoxicated by the liver. Perfusion experiments have shown that little, if any, of the local anæsthetic present in circulating blood is excreted as such by the kidneys, and that most is detoxicated by the liver; a constant fraction of the mass of local anæsthetic present in circulating blood is rendered inactive per unit time by this mechanism. The detoxication of local anæsthetics by the liver is, therefore, the most important method of their clearance from circulating blood, and is an essential prerequisite for their excretion from the body.

Because of the character of the absorption of local anæsthetics into circulating blood from an extravascular site and their clearance from it by the detoxicating action of the liver, the concentration of a local anæsthetic in circulating blood therefore rises to a certain maximal concentration and then decreases in a logarithmic manner. And the concentration of a given local anæsthetic in circulating blood, when accumulation has reached its maximum value, is determined by the mass of local anæsthetic injected, the minute blood flow through the site of injection and the mass detoxicated per unit time by the liver.

The concentration of a local anæsthetic necessary to depress pheral nerves is, however, about six times greater than that blood d to depress the cells of the central nervous system: if a depends han therapeutic dose of a local anæsthetic is injected into through tascular site, the concentration in circulating blood, when

Table 43 also shows the estimated minimum lethal intravenous dose of these five local anæsthetics for a healthy man. These values have been arrived at by comparison with the results of animal experiments and from information culled from the figures of fatalities reported from time to time in current medical literature. This estimated minimum lethal intravenous dose is employed in clinical practice to calculate the maximum dose of a particular local anæsthetic which can be safely used in a particular subject. For example: reference to Table 43 shows that the minimum lethal intravenous dose of procaine for a healthy man of 70 kilos is 0 045 × 70 = 3·15 grams. *The maximum safe dose of procaine for a healthy man of 70 kilos*, injected into an extravascular site other than the spinal theca may be assessed as nine-tenths of the minimum lethal intravenous dose, viz. 9/10 × 3·15 = 2·83 grams.

Since the maximum safe dose of procaine calculated in this fashion is less than its minimum lethal intravenous dose, it follows that toxic manifestations, even of a minor character, are most unlikely to occur in a healthy subject as the result of the absorption of this dose from an extravascular site; and while severe toxic manifestations must be expected following the inadvertent intravenous injection of the whole of this maximum safe dose, in the absence of other factors, *a healthy subject should invariably ultimately recover if the resuscitative measures outlined above are promptly instituted*

Table 44 shows that the maximum safe dose of procaine for a healthy man of 70 kilos, viz. 2·83 grams, is equivalent to 560 c.c. of a ½ per cent. solution, 280 c.c. of a 1 per cent. solution, or 140 c.c. of a 2 per cent. solution Since this is an ample volume of solution to permit an efficient anæsthetic preparation to be produced by infiltration methods for major surgical procedures, procaine can be judged a non-toxic local anæsthetic. For example, not more than 285 c.c. of a ½ per cent. and 60 c.c. of a 1 per cent solution of procaine is required to produce an efficient anæsthetic preparation for a gastrectomy, a total of 2 025 grams of procaine. And it is clear that the use of the minimum lethal intravenous dose of a local anæsthetic to calculate the maximum safe dose for injection into an extravascular site not only makes for a greater measure of safety in clinical practice, but does not detract from the flexibility of a non-toxic local anæsthetic such as procaine.

at a steady rate which produces a fatal depression of the vital medullary centres is termed the *minimum lethal intravenous dose* of that anæsthetic. The smallest mass of a local anæsthetic injected into an extravascular site, which produces fatal depression of the vital medullary centres when maximum cumulation in

TABLE 43.

MINIMUM LETHAL DOSE OF SEVERAL LOCAL ANÆSTHETICS (GRAMS PER KILO OF BODY WEIGHT).

Drug	Rabbits (observed)		Man (estimated)
	Subcutaneous	Intravenous	Intravenous
Nupercaine	0·035 (U)	0 0025 (U)	0 002
Pantocaine	0 020 (FS)	0 0060 (FS)	0 003
Cocaine	0 126 (HB)	0 0149 (HB)	0 015
Stovaine	0·178 (HB)	0 0285 (HB)	0 030
Procaine	0 460 (HB)	0 0550 (HB)	0·045

(FS): Fussganger & Schaumann (1931).
(HB). Hirschfelder & Bieter (1932).
(U). Uhlmann (1929).

circulating blood has occurred, is termed the *minimum lethal dose* of that anæsthetic *for that extravascular site of injection.* Table 43 shows the observed minimum lethal intravenous dose for rabbits of five of the local anæsthetics in common clinical use. It also shows the smallest observed mass of these anæsthetics which must be injected into a subcutaneous site to produce, when maximum cumulation has occurred, a minimum lethal intravenous dose of the anæsthetic in circulating blood. Absorption from a subcutaneous site is relatively slow, for the minute volume of blood flow through the site is meagre and the constant fraction of the mass injected, which is absorbed per unit time, is small. On this account, it is seen that the observed minimum lethal subcutaneous dose for rabbits is about ten times the minimum lethal intravenous dose for these animals In like manner, the minimum lethal dose of a local anæsthetic injected into each and every extravascular site is larger than the minimum lethal intravenous dose.

and may readily exceed the minimum lethal intravenous dose of the anæsthetic. When liver inefficiency is present or suspected, it is therefore imperative to re-assess the maximum safe anæsthetic dose in keeping with the clinical condition of the particular subject, at some value less than nine-tenths of the minimum lethal intravenous dose. When this is done, it may happen that the total volume of local anæsthetic available is less than is required to produce an efficient anæsthetic preparation. If this is the case, local anæsthesia is clearly contra-indicated; for, on the one hand the maximum safe dose for this particular subject is not sufficient to produce an efficient anæsthetic preparation, and, on the other, the production of an efficient anæsthetic preparation is bound to be followed by toxic manifestations.

When a large dose of a local anæsthetic is employed in clinical practice for a major surgical procedure, the subject is rarely weighed or his maximum safe anæsthetic dose calculated, prior to surgical interference. And, in spite of the fact that local anæsthesia is often regarded as the anæsthetic of choice for seriously ill subjects, it is uncommon for the maximum dose to be calculated on the body weight of the subject, much less re-assessed in keeping with his clinical condition. The need for such a routine is stressed by the reports of Mayer (1924), who states: " Reliable statistics are not available, but fatalities [*during local anæsthesia*] appear to be more common than is ordinarily supposed " and " a large proportion of [*local*] anæsthetic accidents . . . are due to mistakes in drugs, concentration and dosage." Experience in Army Commands, where supervision of anæsthesia was possible, confirms this view. In one Command, nupercaine in a 0·5 per cent. solution was twice used in mistake for procaine for infiltration anæsthesia with fatal results, and in another, a fatal result followed the use of a 1 per cent. solution of pantocaine in mistake for procaine. Convulsions produced by overdose or errors of technique are known to have occurred during local anæsthesia in six subjects without fatal termination in a Far-Eastern Command, where liver inefficiency was common; there may have been other instances which were not reported.

Even when mistakes in drugs, concentration and dosage are avoided, fatalities may still occur during local anæsthesia. Clinical experience has shown that toxic symptoms are relatively frequent

The maximum safe dose of nupercaine and pantocaine for a healthy man of 70 kilos calculated in this fashion, together with equivalent volumes of the solutions most commonly used in clinical practice, are shown in Table 44. Having regard to the potency of these two local anæsthetics, relative to procaine, it is seen that the volume of solution equivalent to the maximum safe anæsthetic dose, in each instance, is ample to permit an efficient anæsthetic preparation to be produced by infiltration methods for major surgical procedures. *Used in this fashion, procaine, nupercaine and pantocaine are, therefore, flexible, non-toxic local anæsthetics*

TABLE 44.

THE MAXIMUM SAFE ANÆSTHETIC DOSE AND THE EQUIVALENT VOLUME OF SEVERAL LOCAL ANÆSTHETICS.

Drug	Maximum safe *anæsthetic dose for a* healthy man of 70 kilos	*Equivalent volume of solution*
Procaine	2 83 grams	560 c.c. of ½% solution 280 c c. of 1% solution 140 c.c. of 2% solution
Pantocaine	0 189 grams	283 c.c. of 1 - 1500 solution 189 c c. of 1 - 1000 solution
Nupercaine	0 126 grams	252 c c of 1 - 2000 solution 189 c.c of 1 - 1500 solution 126 c c of 1 - 1000 solution

The maximum safe dose cited in Table 44 applies only to healthy subjects whose rate of detoxication of local anæsthetics is normal. It must be emphasised that the concentration of a local anæsthetic in circulating blood is not determined solely by the mass of anæsthetic entering the blood stream per unit time: an equally significant factor is the mass of anæsthetic cleared from the blood stream per unit time. And when the detoxication of a local anæsthetic by the liver is sluggish and/or faulty, the maximum concentration which this anæsthetic attains in circulating blood in response to a standard dose is greater than in a healthy subject,

adrenaline (0·03 grams of procaine) and with 3 drops of a ½ per cent. solution of cocaine (1 milligram).

Three methods are employed in clinical anæsthetic practice for the use of local anæsthetics. They are:

1. Infiltration anæsthesia.
2. Regional anæsthesia.
3. Spinal anæsthesia.

When infiltration anæsthesia is employed, the local anæsthetic in suitable dilution is injected directly into the vicinity of the peripheral nerve or group of nerves which it is proposed to subject to its action, and the diffusion of the drug from the site of injection to the nerve trunk is relied upon to effect the uptake of the local anæsthetic by the nerve. Regional anæsthesia implies more accurate placing of the local anæsthetic solution and it requires not only an accurate knowledge of the anatomy of the part, but also a knowledge of the technique which must be adopted in each instance to place the injection accurately. The safe and successful use of infiltration and regional anæsthesia depends upon the application of the principles already discussed in this section, combined with a knowledge of local anæsthetic technique. It is not proposed to recapitulate the technique of infiltration and regional anæsthesia, which is admirably dealt with in publications devoted particularly to local anæsthesia. It is proposed, however, to discuss a particular form of regional anæsthesia—spinal anæsthesia—which, it is considered, lies within the particular province of the anæsthetist and introduces problems that have nothing in common with other methods of local anæsthetic administration.

In spinal anæsthesia, the local anæsthetic solution is injected, after lumbar puncture has been successfully performed, into the lumbar cul-de-sac of the spinal subarachnoid space, where it mixes with cerebrospinal fluid and is thus brought into intimate contact with the spinal nerve roots as they cross the subarachnoid space. Fontecilla and Sepulveda (1929) observed the volume of cerebrospinal fluid soon after death in three accident cases, and according to their observations, the average adult volume of cerebrospinal fluid is 128 - 130 c.c. A little more than half this volume is contained in the intraventricular system and the cerebral subarachnoid space, and the remainder, about 60 c.c., is contained in the spinal subarachnoid space. Cerebrospinal fluid is a clear colourless

when local anæsthetics are employed in certain extravascular sites. Thus, toxic symptoms are not infrequent when local anæsthetics are injected into closed mucous or serous cavities, such as the urethra, the bladder, the scrotal sac, etc., or into vascular sites, such as the nasal and tonsillar region. These sites have been regarded, and rightly so, as dangerous regions for the injection of local anæsthetics, but the accidents which occur are associated, not so much with the site itself, as with the pathological conditions present at the site which increase the rate of absorption of the anæsthetic into circulating blood.

It should be realised, too, that adrenaline overdose may occur during local anæsthesia. Adrenaline is an extremely potent drug; its minimum lethal intravenous dose in dogs is about 0·1 milligram, and its minimum lethal subcutaneous dose is about 5 milligram. And when large volumes of a local anæsthetic solution containing adrenaline are employed, abnormally rapid absorption from an extravascular site or the inadvertent intravenous injection of the solution may well result in the entrance of toxic quantities of adrenaline into the blood stream. Adrenaline should never be employed with cocaine, and it is a wise clinical rule never to use more than 15 minims of 1 - 1000 adrenaline in a 1 - 200,000 dilution, irrespective of the volume of local anæsthetic employed It is likely that the excessive absorption of adrenaline or the effect of sympathetic overaction during local anæsthesia may be responsible for unexplained accidents not only with cocaine but also with drugs such as procaine. The subject is usually in some considerable degree of emotional stress; a rising pulse rate is followed by a vagal overaction, and cardiac arrest occurs in diastole. It is significant that this type of accident seldom, if ever, occurs in hospital patients who have been properly prepared. *The importance of adequate pre-medication prior to local anæsthesia cannot be too strongly stressed* Morphia and scopolamine in hypnotic dosage are the usual pre-medicants employed. Barbiturates are valuable pre-medicants, and Clark (1940) stated that they are antagonists to cocaine.

Finally, there are subjects who exhibit a personal and peculiar non-uniformity to the action of local anæsthetics. No explanation can be offered for such idiosyncracy, and death has been reported following 4 c.c. of a $\frac{2}{3}$ per cent. solution of procaine with

liquid, alkaline in reaction, with a specific gravity of 1·003 - 1·007. It has a pH of 7·4 - 7·6 and its alkaline reserve and freezing point are the same as that of blood.

The local anæsthetic solutions used for spinal anæsthesia are clear, colourless, dilute aqueous solutions of the anæsthetic salt. They are neutral or slightly acid in reaction, and their specific gravity varies as the potency of the particular anæsthetic and the presence or absence of added substances. Nupercaine and pantocaine are potent anæsthetics, effective in dilute solutions. Thus, one part of nupercaine added to 1500 parts of water is an effective anæsthetic solution, and the weight of nupercaine in this solution produces little increase in the unit weight of the solution relative to unit weight of water. In fact, a 1 - 1500 solution of nupercaine, to which sufficient sodium chloride has been added to produce a 0 5 per cent. concentration of saline, has a specific gravity of 1·0035 at 15°C and is, therefore, lighter than cerebrospinal fluid. On the other hand, a solution of 1 - 200 nupercaine, to which sufficient glucose has been added to produce a 6 per cent. concentration of glucose, has a specific gravity of 1 024 and is heavier than cerebrospinal fluid Stovaine and procaine are used in a 5 per cent. or a 10 per cent. solution with 6 - 10 per cent. of glucose, and by reason of the weight of drug in solution and the added glucose are heavier than cerebrospinal fluid. Local anæsthetic solutions may also be lightened by the addition of alcohol, and spinocaine which is a 10 per cent solution of procaine, contains 14 5 per cent. of alcohol. It has a specific gravity of 1 005 and is lighter than cerebrospinal fluid, the presence of an amylo-prolamin combination increases the viscosity of the solution. The spinal anæsthetic solutions in common clinical use are thus lighter or heavier than cerebrospinal fluid· and they are termed respectively *hypobaric* and *hyperbaric* solutions.

Cerebrospinal fluid and the local anæsthetic solutions employed in spinal anæsthesia do not form homologous solutions, but they are sufficiently alike to be miscible; the technique of administration of spinal anæsthetics is conditioned by the aim of the anæsthetist, which is either to promote or to hinder the mixing of these two solutions In general, when heavy spinal solutions are used, it is the aim of the anæsthetist to promote mixing; when light spinal solutions are employed, the technique of administration is planned

TABLE 45

THE HEIGHT AND DURATION OF ACTION OF SPINAL ANÆSTHESIA PRODUCED WHEN BARBOTAGE IS EMPLOYED WITH VARIOUS DOSES OF THE SPINAL ANÆSTHETICS IN COMMON CLINICAL USE.

Upper level of Anæsthesia	Procaine 10%	Stovaine 10%	Nupercaine 1 - 200	Nupercaine 1 - 1500
Lumbar 1	2 c.c.	0·6 c.c.	1·4 c.c.	10 c.c. In sitting position for 20 seconds
	Plus barbotage with 1 c.c. of C.S.F.			
Dorsal 10	3 c.c.	0·8 c.c.	1·6 c.c.	12 c.c. In sitting position for 30 seconds
	Plus barbotage with 2 c.c. of C.S.F.			
Dorsal 6 - 4	3 c.c.	1 c.c.	1·8 c.c.	15 c.c. In sitting position for 40 seconds
	Plus barbotage with 3 c.c. of C.S.F.			
Duration of Anæsthesia	30 - 45 minutes	45 - 60 minutes	90 minutes	2½ hours

time, for excessive dilution has been produced. Insufficient barbotage will also produce too low a level of anæsthesia, which will last, however, for an abnormally long period of time, for in this instance the active column of anæsthetic is excessively concentrated. And it is clear that the control of the height of spinal anæsthesia, when barbotage is employed, is neither precise nor accurate. Its basis is at best an intelligent guess; but the guess of an anæsthetist experienced in spinal anæsthesia will be a remarkably accurate one, and has given excellent clinical results over a long period of time.

Heavy spinal solutions are employed without barbotage when so-called "saddle anæsthesia," which involves only the sacral nerve roots, is desired. The spinal solution at room temperature, viz. 1 c.c. of 10 per cent. procaine, 0·3 c.c. of 10 per cent. stovaine or 1·2 c.c. of 1 - 200 nupercaine, is injected slowly without barbotage into the lumbar subarachnoid space with the subject in the sitting position. Since the injected solution is colder and heavier than cerebrospinal fluid, and because it has been injected slowly without producing turbulence, it sinks to the lowest level of the spinal theca where it spreads by diffusion in the cerebrospinal fluid of the lumbar cul-de-sac and produces an effective concentration of the local anæsthetic in cerebrospinal fluid to the level of the first sacral nerve roots. If the sitting position is maintained for about 5 minutes, saddle anæsthesia is produced which lasts for 45 - 60 minutes. If turbulence is avoided during injection, this manœuvre involves only one variable, viz. the mass of local anæsthetic required to produce an effective anæsthetic solution to the level of the first sacral nerve roots. The above figures have been gradually evolved in clinical experience, and the method is both accurate and reliable.

When a light spinal anæsthetic solution, such as nupercaine 1 - 1500, is employed without barbotage, it is the aim of the anæsthetist to bring this solution, *undiluted to any significant extent*, into contact with spinal nerve roots as they cross the spinal subarachnoid space. Light nupercaine solution at room temperature is therefore injected slowly into the lumbar subarachnoid space with the subject lying on his side; because turbulence has been avoided and because the injected solution is colder and lighter than cerebrospinal fluid, it floats to the uppermost lateral boundary of the spinal theca. It assumes the shape of a long narrow bubble of

the nerve roots chosen are bathed by the local anæsthetic as actually injected, undiluted to any significant extent.

Local anæsthetic solutions are also used without barbotage in repeated or fractional dosage. With the spinal needle *in situ*, Sebrecht (1934) used nupercaine 1 - 1500 in fractional doses of 5 c.c. repeated at intervals of 5 minutes until the desired level of anæsthesia had been attained. Using a divided mattress, and a special malleable spinal needle which could be retained *in situ* throughout the whole period of surgical interference, Lemmon (1940) employed 3½ per cent. procaine in doses of 3 c.c. followed by fractional doses when and if desired. Lee (1943) used a hyperbaric solution of 5 per cent. procaine with glucose in a similar manner. Frazer (1943) used a 1 per cent. solution of procaine in fractional doses, and this affords greater protection, for Maxson (1938) asserts that the minimum threshold concentration necessary to depress the phrenic nerves is a 1·25 per cent. solution of procaine.

It can be concluded that more precise and accurate control of local anæsthetic solutions in the spinal subarachnoid space is obtained with methods of administration which avoid barbotage.

When an effective concentration of a local anæsthetic is brought into contact with the spinal nerve roots as they cross the spinal subarachnoid space, the functional activity of these nerves is completely depressed. There is complete blockage of afferent impulses carried to the central nervous system by each posterior spinal nerve root, and of somatic and autonomic efferent impulses carried to the effector organs by each anterior spinal nerve root which is the final common motor pathway of each spinal segment. Hence, sensation and motor tone is completely abolished in each affected segment, and because there is a measure of intersegmental overlapping of autonomic function, autonomic activity is not abolished on a strict segmental basis but is considerably reduced. And if the spinal anæsthetic solution has been accurately placed, an efficient anæsthetic preparation to the desired level is achieved when the spinal nerve roots have been bathed with an effective concentration of the anæsthetic solution for about 5 - 15 minutes.

During the first 5 - 15 minutes after the injection of spinal anæsthetic solutions, changes in the posture of the subject produce characteristic alterations in the level of these solutions in the spinal

local anæsthetic floating on cerebrospinal fluid. In cross-section, this bubble is the segment of a circle whose circumference hugs the uppermost lateral boundary of the spinal subarachnoid space; in depth it is slightly less than the radius of the subarachnoid space, and so bathes the anterior and the posterior nerve roots of the uppermost side. And because of its characteristic cross-section, it will bathe both anterior spinal nerve roots when the subject is placed in the supine position, and both posterior nerve roots in the prone position. The length of this bubble of local anæsthetic varies as the volume of nupercaine 1 - 1500 injected. Howard Jones (1930) calculated the volume of light nupercaine required to produce a bubble of local anæsthetic stretching from the caudal end of the subarachnoid space to the level of the third dorsal nerve roots in the following manner:

The length of the spine in full flexion from the vertebra prominens to the intercristal line is measured in inches. This number, less 4 in males and less 6 in females, indicates the maximum volume of light nupercaine in cubic centimetres to be used in the particular subject in order to produce a light nupercaine bubble stretching to the level of the third dorsal nerve roots, and, in consequence, spinal anæsthesia to this level. Suppose the distance from the vertebra prominens to the intercristal line in an adult male was 20 inches. In this subject, with appropriate alteration of posture, 16 c.c. of light nupercaine would produce spinal anæsthesia to the level of the third dorsal, 12 c c. would produce spinal anæsthesia to dorsal 8, 10 c.c. to the level of dorsal 10, and 6 c.c. to the level of the first sacral nerve roots And in the particular subject, after calculation of the maximum volume of light nupercaine which should be employed to produce the highest level of spinal anæsthesia, the volume is then scaled down in like manner in keeping with the level of spinal anæsthesia required. Thus, if light nupercaine is employed without barbotage, it is possible to calculate the volume of local anæsthetic required in the particular subject to produce a given level of spinal anæsthesia. It is possible, by changes in the posture of the subject from the lateral to the prone and to the supine position, to ensure that the bubble of local anæsthetic bathes and anæsthetises any given combination of spinal nerve roots. Finally, continuity of results will be obtained, for

the nerve roots chosen are bathed by the local anæsthetic as actually injected, undiluted to any significant extent.

Local anæsthetic solutions are also used without barbotage in repeated or fractional dosage. With the spinal needle *in situ*, Sebrecht (1934) used nupercaine 1 - 1500 in fractional doses of 5 c.c. repeated at intervals of 5 minutes until the desired level of anæsthesia had been attained. Using a divided mattress, and a special malleable spinal needle which could be retained *in situ* throughout the whole period of surgical interference, Lemmon (1940) employed 3½ per cent. procaine in doses of 3 c.c. followed by fractional doses when and if desired. Lee (1943) used a hyperbaric solution of 5 per cent. procaine with glucose in a similar manner. Frazer (1943) used a 1 per cent. solution of procaine in fractional doses, and this affords greater protection, for Maxson (1938) asserts that the minimum threshold concentration necessary to depress the phrenic nerves is a 1·25 per cent. solution of procaine.

It can be concluded that more precise and accurate control of local anæsthetic solutions in the spinal subarachnoid space is obtained with methods of administration which avoid barbotage.

When an effective concentration of a local anæsthetic is brought into contact with the spinal nerve roots as they cross the spinal subarachnoid space, the functional activity of these nerves is completely depressed. There is complete blockage of afferent impulses carried to the central nervous system by each posterior spinal nerve root, and of somatic and autonomic efferent impulses carried to the effector organs by each anterior spinal nerve root which is the final common motor pathway of each spinal segment. Hence, sensation and motor tone is completely abolished in each affected segment, and because there is a measure of intersegmental overlapping of autonomic function, autonomic activity is not abolished on a strict segmental basis but is considerably reduced. And if the spinal anæsthetic solution has been accurately placed, an efficient anæsthetic preparation to the desired level is achieved when the spinal nerve roots have been bathed with an effective concentration of the anæsthetic solution for about 5 - 15 minutes.

During the first 5 - 15 minutes after the injection of spinal anæsthetic solutions, changes in the posture of the subject produce characteristic alterations in the level of these solutions in the spinal

subarachnoid space. The raising of the subject's head and shoulders produces a relatively rapid movement of light spinal solutions cranially, while heavy solutions move caudally at a slower rate; when the Trendelenburg position is assumed, heavy spinal solutions move cranially in the spinal subarachnoid space while light solutions move caudally at a relatively rapid rate. The posture of the subject during this period of spinal anæsthesia is thus a valuable means of accurately placing the spinal solution at the desired level, particularly so when hypobaric solutions are used without barbotage. On the other hand, incorrect or careless changes of posture during this period may result in an effective concentration of the spinal solution reaching the cervical region of the spinal subarachnoid space, or even entering the cerebral subarachnoid space. *The dangers of the cranial movement of an effective concentration of a local anæsthetic are very real*, for on the one hand the phrenic nerves may be depressed and respiration paralysed peripherally, and, on the other, an active concentration of the local anæsthetic may enter the fourth ventricle and depress the vital medullary centres.

When the dose and the technique of administration of spinal anæsthetic solutions is correct, the concentration of the anæsthetic in the lower spinal subarachnoid space is fairly rapidly reduced by the uptake of the anæsthetic by nervous tissue, and by its dissociation and dilution by cerebrospinal fluid; in the absence of barbotage, local anæsthetic can reach the cerebrospinal fluid of the upper cervical regions only by diffusion, which is relatively slow. When these considerations are taken with Maxson's view that the phrenic nerves require a greater concentration of a local anæsthetic to depress them than do spinal nerve roots, it is improbable that an effective concentration of spinal anæsthetic is ever reached in the phrenic region of the spinal subarachnoid space *except when gross errors of dosage and technique have occurred* If, however, phrenic paralysis does occur, artificial respiration by oxygen insufflation must be immediately instituted, and if the subject can be adequately oxygenated, respiration will begin spontaneously within 20 - 30 minutes. It must be emphasised that manual compression of the chest wall is a useless procedure, for in the phrenic paralysis of spinal anæsthesia (as in over-curarization) the respiratory muscles are completely paralysed.

To be effective, artificial respiration must consist of the inflation of the subject's lungs with an oxygen atmosphere by manual pressure of the bag of an anæsthetic machine or any other form of inflation apparatus. Clinical experience shows that phrenic paralysis during spinal anæsthesia is rare: but, if gross errors of dosage are combined with excessive barbotage, it could readily occur. The possibility of phrenic paralysis when errors or accidents occur during the Etherington Wilson method of using nupercaine 1 - 1500 must always be one of the grave criticisms of this technique; and although the present writer has had no experience of repeated or fractional spinal anæsthesia, it seems reasonable to suppose that errors or accidents during this method of administration could readily lead to phrenic paralysis.

In a correctly managed spinal anæsthetic, it is even less likely that an effective concentration of the local anæsthetic solution could enter the fourth ventricle, *but it is possible*, and could be produced by an accentuation of any of the factors which have been seen to predispose to phrenic paralysis. Hill and McDonald (1935) have shown in dogs that the direct application of a local anæsthetic to the floor of the fourth ventricle produces immediate respiratory paralysis. When the animal was adequately oxygenated, however, spontaneous respiration re-commenced within 20 - 30 minutes. Hence, whether the origin of respiratory paralysis is peripheral or central, the treatment of this condition is the same in each instance. The airway is cleared, the lungs are rhythmically inflated with an oxygen atmosphere, and analeptic drugs, such as lobeline, may be administered.

About 30 minutes after the intrathecal injection of a local anæsthetic, the posture of the subject may be changed to meet the requirements of the particular surgical procedure and the needs of the surgeon, for after this period of time has elapsed, changes in the posture of the subject no longer produce alterations in the level of spinal anæsthesia. The spinal solution is said to be *fixed* and the Trendelenburg position can be assumed with heavy solutions without fear of phrenic or medullary paralysis. This implies that the concentration of the local anæsthetic is now below the minimum threshold concentration necessary to depress the functional activity of spinal nerve roots, the phrenic nerves and the vital medullary centres. And this dilution of the concentration of the spinal

anæsthetic in cerebrospinal fluid is produced by the uptake of the local anæsthetic by nervous tissue; by the dissociation of the local anæsthetic salt by alkaline cerebrospinal fluid and the subsequent precipitation of the anæsthetic base out of solution in cerebrospinal fluid: by the diffusion of the local anæsthetic throughout the whole volume of cerebrospinal fluid contained in the subarachnoid space; and by the absorption of the local anæsthetic into the blood stream, and its subsequent detoxication and excretion from the body.

Once the fixation of the spinal anæsthetic is complete, any deleterious effects that may occur during spinal anæsthesia are to be attributed on the one hand to the depression of the central nervous system produced by the absorption of a toxic concentration of the local anæsthetic into the blood stream from the site of injection, and on the other, to effects produced by the anatomical nature of the nerve block.

Table 46 shows the maximum anæsthetic dose of four of the most commonly used spinal anæsthetics and the minimum lethal intravenous dose of these four anæsthetics for a 70-kilo man. *It is seen that the greatest dose of these local anæsthetics as used in spinal anæsthesia is one-tenth or less of the minimum lethal intravenous dose of these drugs, and in the case of stovaine it is one-twenty-first part of the minimum lethal intravenous dose.* Since in addition, the absorption of local anæsthetics from the subarachnoid space is not rapid, *it is clear that a toxic concentration of a local anæsthetic cannot enter the blood stream during spinal anæsthesia when standard dosage is employed.* The systemic effects which occur during spinal anæsthesia must, therefore, be attributed to the anatomical nature of the nerve block produced.

During spinal anæsthesia, when a posterior nerve root is blocked as it crosses the spinal subarachnoid space, all forms of sensation served by the posterior nerve are abolished in the following order: first epicritic, then protopathic, and, finally, deep sensibility. Moreover, visceral sensibility in the affected segment is abolished, the superficial and deep reflexes no longer react and muscle tone is diminished. The extent of this sensory loss depends upon the number of posterior nerve roots blocked. But sensory loss, even though it involve the whole body, can produce no harmful effects if the subject is adequately protected from harmful external stimuli: *no harm and much protection accrues during spinal anæsthesia*

TABLE 46.

THE MAXIMUM CLINICAL DOSE OF SEVERAL SPINAL ANÆSTHETICS RELATIVE TO THEIR MINIMAL LETHAL INTRAVENOUS DOSE FOR A 70-KILO MAN

Drug	Maximum Anæsthetic Dose for a 70-kilo man		Minimum Lethal Intravenous Dose for a 70-kilo man	$\frac{\text{M.A.D}}{\text{M.L I.D.}}$
Nupercaine	20 c c of 1 - 1500 2 7 c c of 1 - 200	(0 0133 gm.)	0·14 gm.	$\frac{1}{10}$
Procaine	2 c.c. of 10%	(0·2 gm.)	3·15 gm.	$\frac{1}{16}$
Stovaine	1 c.c of 10% 2 c c. of 5%	(0·1 gm.)	2 1 gm.	$\frac{1}{21}$
Pantocaine		(0 0204 gm)	0 21 gm	$\frac{1}{10}$

when a sufficient number of posterior spinal nerve roots are blocked and a high level of sensory loss is produced.

In contrast, extensive and serious results follow the depression of the functional activity of anterior spinal nerve roots during spinal anæsthesia. Each pair of anterior spinal nerve roots represents the final common pathway of all efferent fibres emerging from this particular segment of the spinal cord, and they contain motor fibres to skeletal muscles and sympathetic vaso-constrictor fibres to the blood vessels. It follows that the field of peripheral resistance paralysed, and the extent of the loss of motor tone—which is absolute, for this is a lower motor neurone lesion—will vary as the number of anterior spinal nerve roots blocked by the spinal anæsthetic. Loss of peripheral resistance can be compensated only by an increase of cardiac output, but complete loss of muscle tone over a wide field, combined with shallow breathing, eventually retards the return of venous blood to the right heart, and so diminishes the cardiac output. These deleterious factors combine to produce a fall of blood pressure—for, in its simplest terms, blood pressure is the product of cardiac output and peripheral resistance. The intensity of the fall of blood pressure and, in turn, the degree of cardiovascular embarrassment during spinal anæsthesia vary as the clinical condition of the cardiovascular system of the particular subject prior to spinal anæsthesia and the number of anterior spinal nerve roots paralysed during spinal anæsthesia *And it can be concluded that the ideal spinal anæsthetic is one in which a sufficient number of posterior spinal nerve roots are paralysed to produce a high level of sensory loss, while the number of anterior spinal nerve roots paralysed is the smallest compatible with the nature of the proposed surgical procedure*

In the past, spinal anæsthesia has often been considered the anæsthetic of choice for very sick subjects; this view is no longer held, but it is often very difficult to decide whether spinal anæsthesia is a suitable anæsthetic for a particular subject. In answering this question, the deciding factor is the condition of the cardiovascular system of the particular subject. Bearing in mind the lowered metabolic rate of the subject during spinal anæsthesia, the anæsthetist must decide whether the cardiovascular system is or is not capable of compensating for the field of peripheral

resistance which will be abolished, and the degree of diminished venous return which will be produced, by the level of spinal anæsthesia required for the proposed surgical procedure. If it is considered that the necessary compensation is possible, spinal anæsthesia is a suitable anæsthetic. If, however, the pathological condition of the cardiovascular system suggests that such compensation is not possible, it is wise to avoid spinal anæsthesia. In such a subject, fatal cardiovascular collapse may occur during spinal anæsthesia; but it is more likely, surgical interference having been successfully completed, that the subject will develop cardiovascular distress early in the post-anæsthetic period with fatal cardiac failure and/or fatal hypostatic bronchopneumonia. The field of clinical usefulness of spinal anæsthesia can, however, be enlarged in a measure when light spinal solutions are used without barbotage. Thus, when the Howard Jones technique of using nupercaine 1 - 1500 is employed, it is possible to produce a high level of sensory loss with a much lower level of paralysis of anterior spinal nerve roots; and when the modification of this technique, described by Harris and Rink (1937), is employed, the unilateral paralysis of anterior spinal nerve roots reduces still further the possibility of cardiovascular embarrassment.

During spinal anæsthesia, a material and significant fall of blood pressure may be caused by psychic factors, and adequate premedication is a necessary adjunct to spinal anæsthesia. But in spite of adequate premedication, it may be necessary in certain subjects to produce loss of consciousness with blood-borne anæsthetics such as pentothal, nitrous oxide or ethylene, if the psychic factors are to be controlled. Because of its tendency to produce cardiac arrythmias, it is thought that cyclopropane is not a proper agent to be used during spinal anæsthesia. If psychic factors have been controlled, fall of blood pressure during spinal anæsthesia in an adequately oxygenated subject is due to the inability of the heart to compensate adequately for the diminished field of peripheral resistance and the diminished volume of venous return. When fixation of the spinal anæsthetic has been attained, one of these factors, the field of peripheral resistance paralysed, is a constant; but the other, the volume of venous blood returned to the right heart and (in turn) cardiac output, may be influenced in an upward or a downward direction, with a consequent rise or

fall in the blood pressure of the subject. Hence, in clinical practice, the methods adopted to maintain an adequate blood pressure during spinal anæsthesia are based on those factors which maintain the efficiency of the myocardium and which increase the return of venous blood to the right heart. Nothing depresses the functional activity of the myocardium so rapidly as anoxia, and oxygen should be administered during spinal anæsthesia, when and if this is necessary to oxygenate the subject adequately. The most rapid, effective and rational way of increasing the return of venous blood to the right heart is the use of gravity, and when once the fixation of the spinal anæsthetic has been attained, this is effected by placing the subject in the Trendelenburg position. In 240 consecutive high spinal anæsthetics with nupercaine 1 - 1500, adequate oxygenation of the subject, combined with the minute-to-minute regulation of posture, was the only treatment required to maintain an adequate blood pressure during spinal anæsthesia. Pressor substances such as ephedrine gr. 1½, are often used prophylactically before the injection of the spinal solution, and are used during spinal anæsthesia to produce a rise of blood pressure; but their action is necessarily transient and they cannot be considered as a substitute for adequate oxygenation and posture. The continuous adrenaline 1-250,000 intravenous drip described by Evans (1944) has proved to be of real value during spinal anæsthesia, and this is to be expected, for adrenaline is the chemical transmitter of the sympathetic system and produces local vaso-constriction. An increase of the carbon dioxide content of inspired air also results in a rise of blood pressure during spinal anæsthesia. It increases the cardiac output and stimulates the vasomotor centre directly, and indirectly through the chemo-receptors in the arch of the aorta and the carotid body. But its stimulating effects are transitory, for it soon depresses the conducting mechanism of the heart and heart block, a slow ventricular rate and a fall of blood pressure then occur

Sphygmomanometer readings are of little use in estimating the efficiency of the cardiovascular system during spinal anæsthesia. For example, when spinal anæsthesia has reached the level of dorsal 4, it is impossible to estimate a threshold of effective blood pressure for a premedicated subject whose metabolic rate has fallen to a level which in the particular subject corresponds with this

degree of paralysis of posterior and anterior spinal nerve roots. In the particular subject, the colour and speed of the capillary return in response to pressure, in areas suitable for observation (such as the lobe of the ear), serve as reliable guides that the oxygen-carrying capacity of blood is adequate and that blood is circulating effectively, that the central control of vasomotor tone is efficient, and that the blood pressure, whatever its value in terms of millimetres of mercury, is adequate to the efficient oxygenation of the subject. Digital impressions of the rhythm, the rate and the pressure of the pulse give added minute-to-minute information of the response of the cardiovascular system. A slow pulse, characteristic of a high spinal anæsthetic with nupercaine 1 - 1500, may be due to a heart block, and if this is so, the oxygenation of the subject would soon suffer. As a general rule, a slow pulse during spinal anæsthesia indicates effective cardiac compensation to the diminished field of peripheral resistance, with prolongation of diastole, increased filling of the right heart and, in consequence, an increased cardiac output. On the other hand, an increase of the pulse rate is indicative of a heart labouring ineffectively to produce an increased cardiac output. And a rising pulse rate during spinal anæsthesia indicates cardiovascular distress and is the precursor of a fall of blood pressure below the threshold necessary to oxygenate the subject adequately.

The sequelæ of spinal anæsthesia can be attributed on the one hand to the results of lumbar puncture, and on the other, to effects produced by the spinal anæsthetic solutions injected into the subarachnoid space.

An inept lumbar puncture may be followed by hæmorrhage into the subarachnoid space, injury to the spinal cord or spinal nerve roots, backache, a collapsed intervertebral disc or arthritis of the spine, and severe headache with, perhaps, nausea and vomiting. When, however, a clean lumbar puncture is made with a fine short bevel needle in the mid-line of the interspace between the third and fourth lumbar vertebrae, the spinal cord cannot be injured and trauma of any sort is unlikely. This is particularly so if the stilette of the lumbar puncture needle is removed when the point of the needle reaches the peridural space and before it pierces the subarachnoid membrane. In this instance, cerebrospinal fluid

flows as soon as the short bevelled needle enters the subarachnoid space, and one is unlikely to injure the nerves of the cauda equina, much less to approach the anterior boundary of the subarachnoid space; hæmorrhage or injury to intervertebral discs and vertebral bodies is thus avoided. Backache is unlikely to follow a clean lumbar puncture with a fine needle, but may be produced during spinal anæsthesia by the rough positioning of aged subjects in awkward postures, such as the lithotomy position. The etiology of headache after lumbar puncture is still uncertain. It is often severe and may last for days. Bagley (1928) suggested that hæmorrhage into the subarachnoid space produced meningeal irritation, and this may well be a factor. The most popular explanation is the seepage of cerebrospinal fluid through the lumbar puncture wound into the peri-dural space. Erskine and Johnson (1938) observed that the incidence of lumbar puncture headache decreased as the size of the needle and the dexterity of the surgeon. In an examination of 500 lumbar punctures, Underwood (1946) found that 19 per cent. were followed by headache, and he states that neither sedation nor rest in bed following lumbar puncture reduced the incidence or curtailed the severity of the headache. Evans (1929) and Sheepe (1934) both state that the pressure of cerebrospinal fluid during the period of headache is lower than at the time of the first lumbar puncture, which suggests that seepage from the lumbar puncture wound is sufficient to reduce significantly the pressure of cerebrospinal fluid in the subarchnoid space. The peri-dural space is in the nature of a serous cavity extending from the foramen magnum to the lower border of the second sacral vertebra which normally contains a very small amount of lymph at a negative pressure. It accommodates the spinal theca when, due to increased venous pressure caused by emotion, etc , the secretion of cerebrospinal fluid and, in turn, the pressure of cerebrospinal fluid in the subarachnoid space are suddenly increased. During peri-dural anæsthesia, up to 30 c.c. of local anæsthetic solution are injected into this space, and it could probably accommodate 50 c.c. of fluid without appreciably compressing the contents of the spinal theca. Cerebrospinal fluid is a dialysate whose formation and pressure is particularly related to intracranial venous pressure, upon which intracranial capillary pressure so closely depends, and the whole volume of cerebrospinal

fluid, viz. 130 c.c., is normally replaced 4 - 6 times daily and the rate of its secretion may be increased to 1000 c.c. each 24 hours. Because of the rate of secretion of cerebrospinal fluid, and since seepage of cerebrospinal fluid must cease as soon as its pressure in the peri-dural space equals that in the spinal subarachnoid space, it is difficult, even if it is assumed that absorption from the peri-dural space is rapid, to suppose that leakage through a fine lumbar puncture wound could produce a lasting fall of pressure of cerebrospinal fluid in the subarachnoid space, much less a fall of the significance required to produce headache of the severity and duration that sometimes follows lumbar puncture. And it is significant in departments of venereology where frequent diagnostic lumbar punctures are performed, that a spate of lumbar puncture headaches is invariably traced to a minor error of technique introduced with change of staff, etc. Thus, Dr. V. E. Lloyd (1948) recently traced such an outbreak to the presence of tiny charred carbon particles in lumbar puncture needles. These needles were packed with their points impinging on a pad of cotton wool, and tiny particles of this wool found their way into the needles. When autoclaved, the wool became charred and provided the irritant which, introduced into the spinal subarachnoid space, produced headache; when cotton wool was eliminated from the containers, the lumbar puncture needles no longer contained carbon particles, and post-lumbar puncture headaches ceased.

When trauma due to lumbar puncture is avoided, spinal meninges, spinal nerve roots, the spinal cord and, indeed, even the cerebral meninges and cranial nerves may be infected, irritated or occasionally irreversibly damaged during spinal anæsthesia.

Fatal meningitis has been reported following spinal anæsthesia, and Barrie (1941) reported eleven cases of low grade meningitis of bacterial origin in a series of ninety-six spinal anæsthetics. When sepsis occurs, the source of infection is to be found in the skin, the spinal equipment used, the spinal solution injected or in the technique of administration. A rigid aseptic technique should, therefore, be adopted, the skin should be thoroughly cleansed, a skin incision, larger than the spinal needle to be introduced, should be made, or a Sise introducer employed; and the spinal solution should be above suspicion bacteriologically.

When, however, the technique of administration is faultless,

lesions ranging in severity from gangrene of the spinal cord to headache still occur in the post-anæsthetic period. Thus, gangrene of the lumbar region of the spinal cord has been observed at autopsy after spinal anæsthesia with stovaine and spinocaine; Martin (1937) and Elstad (1936) have reported ascending myelitis after spinal anæsthesia. Palsies in many nerves, usually in those of the lower limbs, have frequently been reported, and lesions have been observed in all the cranial nerves except the olfactory, the vagus and the glossopharyngeal nerves. The abducens is the cranial nerve most commonly involved, and squint, diplopia, photophobia, aphasia and deafness may occur 3 - 8 days after spinal anæsthesia Cauda equina lesions are also relatively common after spinal anæsthesia, with loss of sensation and trophic changes in the saddle and sacral areas, retention of urine, incontinence of fæces, and loss of sexual function. Watkins (1938) had thirteen such cases with heavy duracaine *in as many months. These lesions are sometimes* transient, sometimes permanent. But the commonest complication of spinal anæsthesia is post-anæsthetic headache, occurring in from 2 - 40 per cent. of cases, according to various observers.

Lesions may be due to the irritating properties of the injected spinal solution Davis *et al.* (1931) and Iason *et al.* (1930) have observed a constant meningeal reaction of varying intensity after the injection of spinal solutions such as nupercaine and procaine, and the intensity of the reaction was greater when large doses of spinal solution were injected. There is a growing realization that concentrated solutions of local anæsthetics in cerebro-spinal fluid are more likely to produce trauma to meninges and/or nervous tissues than are weak solutions. When the technique of administration is correct, a *high concentration* of a local anæsthetic in cerebrospinal fluid is not necessary for efficient anæsthesia, for using fractional methods of injection, Frazer (1943) produced efficient spinal anæsthesia in which the concentration of procaine in cerebrospinal fluid could not have been greater than 1 per cent.

It is difficult, however, to attribute the nervous lesions which occur after spinal anæsthesia solely to a high concentration of the spinal anæsthetic solution injected, for hundreds of thousands of spinal anæsthetics have been administered in clinical anæsthetic practice without mishap, using these standard anæsthetic solutions. It is significant, too, that a given local anæsthetic injected into a

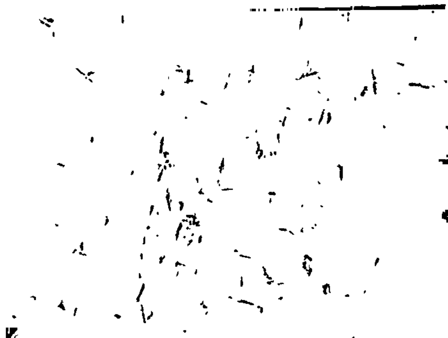
peripheral nerve during regional anæsthesia in the same concentration as is used in spinal anæsthesia, rarely if ever produces nervous lesions of this character. If a high concentration of the local anæsthetic was the sole cause of the nervous sequelæ of spinal anæsthesia, this might logically explain the relatively high incidence of cauda equina lesions when a heavy spinal solution was used, but could not explain the incidence of particular cauda equina lesions, for sometimes the nerves of the bladder are affected, at other times the rectal, and/or sensory or trophic nerves. While particular cauda equina lesions might be explained from the individual susceptibility of particular nerve roots, the haphazard incidence of the involvement of particular nerve roots eliminates individual susceptibility as a relevant factor. Finally, the involvement of the cranial nerve roots, two or three days after the administration of the spinal anæsthetic, seems to eliminate completely either a high concentration of local anæsthetic *per se*, or individual susceptibility, as a relevant factor. It appears, therefore, that a set of circumstances is present during spinal anæsthesia that has no parallel when local anæsthetics are injected into other extravascular sites, and this is, in fact, the case.

When a local anæsthetic solution is injected into the spinal subarachnoid space, it comes into contact with cerebrospinal fluid whose pH is 7·4 - 7·6 and whose alkali reserve is the same as that of blood, and dissociation of the anæsthetic salt occurs with liberation of the anæsthetic base. The extent of this dissociation depends upon the volume of alkaline cerebrospinal fluid brought into contact with a given volume of local anæsthetic solution of standard concentration. When large volumes of standard spinal anæsthetic solution are mixed with large volumes of cerebrospinal fluid, or when cerebrospinal fluid is more alkaline than normal, the release of anæsthetic base in cerebrospinal fluid is correspondingly increased. This dissociation of the anæsthetic salt is in the nature of a titration, and when the total alkali in the cerebrospinal fluid in contact with the anæsthetic salt has been depleted, the release of anæsthetic base proceeds more slowly, for diffusion of the local anæsthetic in cerebrospinal fluid is relatively slow and the circulation of cerebrospinal fluid in the spinal subarachnoid space is sluggish. Clinically, the release of free anæsthetic base is manifest as a cloudiness in the solution when cerebrospinal fluid

is aspirated into the spinal anæsthetic solution of the syringe during administration. During in vitro experiments with cerebrospinal fluid and standard spinal anæsthetic solutions, cloudiness occurs on mixing, and then colourless crystals of freed nupercaine, stovaine or procaine base settle to the bottom of the test tube. Examined microscopically, each crystalline base has a characteristic shape; Figure 12 is a microphotograph of the crystals of nupercaine base, magnification × 80.

Reference to Figure 12, however, shows that the size of the crystals of nupercaine base precipitated by the same volume of cerebrospinal fluid varies as the concentration of the local anæsthetic solution, *and the crystals precipitated from a* 1 - 200 *solution of nupercaine are about four times larger than those precipitated from a* 1 - 1500 *solution of nupercaine.* These crystals of nupercaine base have proved to be very insoluble in water, and (it is presumed) very soluble in lipoid, for even when subjected to the heat of the illumination necessary to take these microphotographs, they did not dissolve in the aqueous medium, and it was possible to obtain these pictures. Crystals of stovaine and procaine however, are more soluble in water than nupercaine base, for while discrete crystals could be examined microscopically at room temperature, they dissolved in the aqueous medium when subjected to the heat of the illumination required for microphotography, but precipitated out of solution again when placed in an icebox. The presence of cells in one sample of cerebrospinal fluid appeared to hold crystals of procaine base in suspension even when heated, which suggests that inflammatory conditions of the arachnoid membrane, or the presence of substances added to spinal solutions such as amylo-prolamin, or irritants such as alcohol or glycerine, may prolong the period of suspension in cerebrospinal fluid of even (relatively) water-soluble stovaine or procaine base.

Since body tissues are alkaline in reaction, dissociation of the anæsthetic salt with liberation of the anæsthetic base, occurs therefore whenever a local anæsthetic is injected into body tissues. The spinal subarachnoid space, however, differs from all other extravascular sites of injection, for the movement of crystals of anæsthetic base released into cerebrospinal fluid is free and unrestricted within the whole volume of the subarachnoid space.



A.



B.

FIGURE 12.

1 - 1500 nupercaine base × 80 A	1 - 200 nupercaine base × 80. B.

Crystals of nupercaine base obtained when 2 c c of nupercaine solution were added to 4 c c. of C S F. at room temperature.

Gros found that the anæsthetic activity of local anæsthetics varied as the oil/water partition coefficient of their free anæsthetic bases, and free anæsthetic base is about 4 - 8 times more potent than the corresponding salt. Hence, during spinal anæsthesia, there is reason to believe that potent free anæsthetic base, relatively insoluble in water, but freely soluble in lipoid, is present in cerebrospinal fluid either in the form of a fine suspension as in Figure 12A, or aggregated into larger particles as in Figure 12B. There is no reason to doubt that a fine suspension of free anæsthetic base is beneficial, and when this occurs, the uptake of the base by nervous tissue is swift and uniform, efficient anæsthesia of equal intensity is produced throughout, and nervous sequelæ in the post-anæsthetic period are most unlikely. Evidence has been discussed which suggests that when large particles of anæsthetic base are precipitated out of solution in cerebrospinal fluid, faulty anæsthesia may be produced by excessive dilution. But it can also be supposed that such large particles of potent anæsthetic base may be deposited upon individual nerve roots as they cross the subarachnoid space. In this instance, the uptake of a relatively large mass of potent anæsthetic base by a small section of the nerve could occur, for the base is freely soluble in lipoid. Consequently, serious and even irreversible injury to the nerve may result. The deposition of large particles of anæsthetic base on individual nerve roots is an attractive hypothesis for the causation of the nervous sequelæ of spinal anæsthesia.

The haphazard incidence of nerve root and cauda equina lesions after spinal anæsthesia has always been inexplicable. The incidence of lesions in these nerves after spinal anæsthesia are of the same order as when traumatic material is dropped on a bundle of nerve roots with a pepper-pot; and a shower of large crystals of anæsthetic base precipitated out of solution in cerebrospinal fluid could be expected to produce an incidence of nerve lesions of a similar order. The delayed onset of cerebral nerve lesions could be explained by the time taken for crystals of the anæsthetic base to reach the cerebral subarachnoid space and the incidence of involvement of particular cerebral nerves to their position in the current of cerebrospinal fluid which flows across the base of the brain. Cerebrospinal fluid emerging from the spinal subarachnoid space, at the anterior lip of the foramen magnum, joins the current

of cerebrospinal fluid which sweeps from the foramena of Magendi and Luschka, forwards and upwards across the base of the brain to be absorbed in the venous sinuses from the vertex to the base of the skull. Crystals of anæsthetic base carried in this stream of cerebrospinal fluid are most likely to be deposited on the abducens nerve, for it has a long intracranial course and lies nearest the mid-line—and in consequence in the long axis of this current—throughout most of its intracranial course. And the position of the occulo-motor, the hypoglossal, the trochlear, the facial, the auditory and the trigeminal nerves at the base of the brain makes the deposition of crystals on them from this stream probable, but less likely, while the position of the vagus and glossopharyngeal nerves and the size of the optic and the olfactory nerves makes involvement from this cause unlikely. Thus, the deposition of crystals of the anæsthetic base could well produce all the nervous sequelæ of spinal anæsthesia, and the size of the crystals deposited could account for the intensity of these lesions, ranging as they do from headache, probably produced by mild meningitis, to irreversible nerve injury.

If the deposition of large aggregates of anæsthetic base is, in fact, the cause of the nervous sequelæ of spinal anæsthesia, their incidence and severity may be reduced by the use of dilute spinal solutions. When excessive cloudiness is seen prior to the injection of the spinal solution—and this indicates excessive alkalinity of cerebrospinal fluid—spinal anæsthesia should be abandoned, if these post-anæsthetic nervous complications of spinal anæsthesia are to be avoided

It can be concluded that safe and efficient anæsthesia may be produced with spinal anæsthetics, but that unpredictable nervous sequelæ, often serious and sometimes irreversible in character, may also occur. Spinal anæsthesia, however, lacks the flexibility of blood-borne anæsthesia To be effective it must be absolute, and its duration is determined by the character of the particular spinal anæsthetic employed Perhaps the most difficult problem is to decide whether the subject is suitable for this form of anæsthesia. If this question is answered correctly, spinal anæsthesia is a safe procedure in the hands of an experienced anæsthetist, but the varying mortality figures of this form of anæsthesia indicates that errors of clinical judgment and/or of the technique of adminis-

tration, once made, cannot be corrected. Thus, Saunders (1931) reported a mortality of one in 200, Babcock (1932) in a series of 15,652 cases, a mortality of one in 400; and Veal *et al.* (1936) in a series of 33,811 cases, a mortality of one in 1127. Reference to Table 42 shows that only the intravenous barbiturates have a mortality rate approaching these figures. Just as the mortality figures of intravenous barbiturates are not a measure of their safety in the hands of an experienced anæsthetist, so also these figures are not indicative of the safety of spinal anæsthetics in experienced hands, and several colleagues of experience whose individual series of cases are of necessity small, have not to date had a death during spinal anæsthesia. And one is led to the conclusion that the safety of spinal anæsthesia depends in a large measure upon the clinical experience of the administrator.

When to this is added the unpredictable and uncontrollable nervous sequelæ which may occur after spinal anæsthesia, its use in clinical practice must be viewed with some degree of trepidation. Since the introduction of curare, many anæsthetists have modified their opinion of the suitability of spinal anæsthesia in clinical practice. In the present writer's practice, spinal anæsthesia is now confined solely to the production of a sacral nerve block for retrograde pyelography, with 0·6 c.c. of 5 per cent. stovaine; when the contemplated surgical procedure requires muscular relaxation, this is almost always produced with d-tubo-curarine chloride combined with a suitable blood-borne anæsthetic to the level of complete sensory loss.

References.

1 Adams, R., Rideal, E K., Burnett, W. R, Jenkins, R. L., and Dreger, E E (1926) *J Amer chem. Soc.* 48, 1758.
2 Balcock, M E (1932) *Anesth & Analges.* July. p. 187
3 Bagley, C (1928) *Arch Surg Chicago.* 17, 28.
4 Barrie, H J (1941) "Lancet" i, 242.
5 Clark, A J. (1940) "Applied Pharmacology" 7th Ed p 282. J & A Churchill, Ltd., London
6 Davis, L, Haven, H, Givens, J. H, and Emmett, J (1931) *J. Amer. med Ass.* 97, 1781.
7 Elstad, D (1936) *Norsk Mag Loegevidensk.* Sept. p. 959
8 Erskine, D, and Johnson, A G (1938) "Lancet." ii, 371.
9 Evans, C H. (1929) "Spinal Anæsthesia." p 126. William Heinemann, Ltd London
10 Evans, F. (1944). "Lancet" I, 15
11. Evans, W V, and Benedict, M C (1930). *Abst. Div. Med. Chem Amer. Chem Soc.*

12 FONTECILLA and SEPULVEDA. Quoted from "Cerebro-spinal Fluid." London. Levinson, A. (1929). p. 89. C. V. Mosby Co., St. Louis
13. FRAZER, R. J. (1943) *Anesth. & Analges.* Jan.-Feb. p. 38.
14. FUSSGANGER, R., and SCHAUMANN, O. (1931). *Arch. exp. Path. Pharmakol* 160, 53.
15. GERLOUGH, T. D. (1931). *J. Pharmacol.* 41, 307.
16 GROS, O. (1910). *Arch. exp. Path. Pharmakol.* 62, 381.
(1910). *Arch. exp. Path. Pharmakol.* 63, 80.
17. HARRIS, T A. B., and RINK, E. H. (1937). Guy's Hosp. Rep 87, 1.
18. HEWER, C L. (1946). "Recent Advances in Anæsthesia and Analgesia" 5th Ed. p. 148. J. & A. Churchill Ltd., London.
19. HILL, E. F., and McDONALD, A. D. (1935). *J. Pharmacol.* 53, 454.
20 HIRSCHFELDER, A. D., and BEITER, R. N. (1932). *Physiol. Rev.* 12, 263.
21. IASON, A. H., LEDERER, M., and STEINER, M. (1930). *Surg. Gynec. Obstet.* 51, 76.
22. JONES, W. HOWARD (1930). *Proc R. Soc. Med.* 23, 919.
23 KATO (1924) "Decrementless Conduction." Tokyo.
24. KOCKMANN, M , and HURTZ, A. W. (1923). *Arch exp. Path. Pharmakol* 96, 372.
25. LEE, J. A (1943). "Lancet." i, 156.
26. LEMON, W. T (1940) *Ann Surg* Jan. p. 141.
27. LLOYD, V. E. (1947). Personal communication.
28. MARTIN, J. P. (1937). *Proc R. Soc Med.* 30, 1032.
29. MAXSON, L. (1938). "Spinal Anæsthesia." J. B. Lippincott Co., Phila.
30. MAYER, E. (1924). *J. Amer. med Ass.* 82, 876.
31 ROHDE, E (1921). *Arch. exp. Path. Pharmakol.* 91, 173.
32 SAUNDERS, E. W (1931). *Ann. Surg.* Noe p 931.
33. SEBRECHTS, J. (1934). *Brit. J. Anæsth* Oct. p. 4.
34. SHEPPE, W M. (1934) *Amer. J. med. Sci* 188, 247.
35. UNDERWOOD, L. J. (1946). *Amer. J Syph.* 30, 264
36 UHLMANN, F. (1929). *Narkose u. Anæsth.* June 15th. 11.
37 VEAL, J. R. et Al (1936). *Amer. J. Surg* Dec p. 606.
38 VLEIT, E B , and ADAMS, R. 1926). *J. Amer. chem Soc.* 48, 2158.
39 WATKINS, K H , and FERGUSON, F. R (1938). *Brit. J Surg.* 25, 735

PART THREE

THE CO-RELATION OF THE LEVEL OF ANÆSTHETIC DEPRESSION OF THE NERVOUS SYSTEM WITH ANÆSTHETIC SLEEP; LOSS OF SENSATION AND LOSS OF MUSCLE MOVEMENT AND MUSCLE TONE

CHAPTER XIX

INTRODUCTION

IN the preceding sections of this discussion, the mode of action of some of the typical anæsthetics in common clinical use has been reviewed. The factors influencing the rate, the mechanism, and the sequence of the uptake of blood-borne anæsthetics by the different parts of the nervous system have been discussed. Evidence has been advanced which indicates that the blood-borne anæsthetics in common clinical use depress, or can be made to depress, the functional activity of the central nervous system level by level in a definite sequence, and inhibit in turn emotional activity, sensation, muscle tone, and finally the functional activity of the vital medullary centres This simplified conception of the levels of functional activity of the brain serves a useful clinical purpose. Moreover, it accords with the thesis that during evolutionary development the higher centres have become dominant over the more primitive caudal centres and that as the higher centres are inhibited, the lower centres are progressively released. It must be understood, however, that many specific functions are represented at each level and that neither emotional activity, nor sensory co-ordination, nor motor co-ordination is a separate entity located at a particular level. Parts of each total mechanism are to be found at various levels, and the control of a function such as blood pressure is represented at each level of functional activity from the spinal cord to the cerebral cortex. Moreover, the autonomic division of the nervous system can no longer be regarded as a purely peripheral system. In normal conditions of life, interaction between the somatic and the autonomic nervous systems is pronounced, and somatic and autonomic entities are to be found at each level of functional activity of the central nervous system. At a given level the somatic system may be dominant and overshadow its autonomic component while at another level the reverse may be the case But in normal conditions of life, the two systems interact harmoniously, and at a

given level a somatic reflex is almost invariably accompanied by its autonomic reflex of central origin. Fulton (1938) gives the following examples of concomitant somatic and autonomic reflexes at various levels: in the spinal cord, the mass reflex; in the medulla, the vasomotor accompaniments of nociceptive reflexes; in the hypothalamus, heat regulation includes panting as well as sweating and vasomotor control; and at the strial and cortical levels, the intermingling of somatic and autonomic reactions is even more extensive. It seems pertinent, therefore, to attempt to trace in greater detail the orderly depression of the individual entities of the somatic and autonomic systems when the standard sequence of anæsthetic depression which is shown in Table 34, obtains. The discussion which follows first refers to the standard sequence of anæsthetic depression of the nervous system produced by blood-borne anæsthetics, such as di-ethyl ether, and distortions of this standard sequence of depression by the other anæsthetics in common clinical use are noted and discussed.

CHAPTER XX

THE STANDARD SEQUENCE OF DEPRESSION OF THE CENTRAL NERVOUS SYSTEM DURING BLOOD-BORNE ANÆSTHESIA

CUSHNY stated that "No poison is known that circulating in blood affects nerve fibres directly; all effects . . . . have been proved to arise at the origin of the neurons in the central nervous system or at their termination in the periphery." Data have been discussed which indicate that this is in fact so with blood-borne anæsthetics. In this discussion, which firstly concerns di-ethyl ether, it is assumed throughout that the concentration of the anæsthetic in circulating blood and, in turn, in the body tissues, is an effective concentration for the cells of the central nervous system, but is at the same time below the threshold concentration necessary to depress the functional activity of nerve fibres.

During di-ethyl ether anæsthesia, memory for recent events is the first function to be inhibited and the subject enters the stage of co-operative stupor. In primates bi-lateral ablation sharply restricted to the frontal association areas (areas 9, 10, 11 and 12 of Brodmann's classification), produces loss of memory of recent events and diminution of the ability to concentrate, but there is no obvious effect on the special senses, on sensation, on motor function, or on the vital medullary centres. This suggests that the *cells of the frontal association areas of the brain are the first cells* to be completely depressed during blood-borne anæsthesia; this level of anæsthesia has been termed the stage of AMNESIA.

With the depression of the frontal association areas as anæsthesia deepens, the subject enters the stage of CO-OPERATIVE STUPOR which has been described as a state of happy inebriation. In this state, some degree of association and co-ordination, synthesis, is still possible, but the ability to concentrate is failing and cerebration is slow. Voluntary eye movements are present but, because the subject's ability to concentrate is failing, fixation is sluggish. For the same reason, auditory localisation and the

given level a somatic reflex is almost invariably accompanied by its autonomic reflex of central origin. Fulton (1938) gives the following examples of concomitant somatic and autonomic reflexes at various levels: in the spinal cord, the mass reflex; in the medulla, the vasomotor accompaniments of nociceptive reflexes; in the hypothalamus, heat regulation includes panting as well as sweating and vasomotor control; and at the strial and cortical levels, the intermingling of somatic and autonomic reactions is even more extensive. It seems pertinent, therefore, to attempt to trace in greater detail the orderly depression of the individual entities of the somatic and autonomic systems when the standard sequence of anæsthetic depression which is shown in Table 34, obtains. The discussion which follows first refers to the standard sequence of anæsthetic depression of the nervous system produced by blood-borne anæsthetics, such as di-ethyl ether, and distortions of this standard sequence of depression by the other anæsthetics in common clinical use are noted and discussed.

depressed, voluntary movement soon ceases but the cruder types of movement patterns are still possible. This in turn gives way to increased reflexes, spastic skeletal muscles with lengthening and shortening reactions, and a positive babinski, and it can be assumed that the anæsthetic depression of area 4 is soon followed by the depression of the cells of area 6.

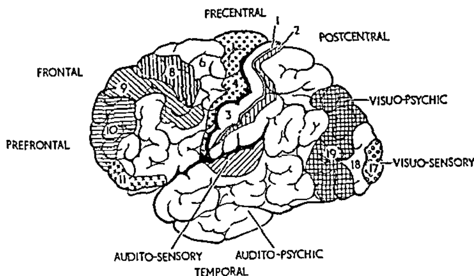


FIGURE 13

Voluntary eye movements soon cease and are replaced by symmetrical or asymmetrical movements of the eyes which may be convergent, divergent, or vertical in character, and are accompanied by diplopia and dizziness. They are attributed to lack of co-ordination of the extrinsic muscles of the eyes and suggest that fixation is no longer possible and that the cells of the frontal eye field, area 8, are now depressed. These irregular and occasional eye movements are soon replaced by a symmetrical, involuntary, worm-like arrythmic movement of the eyes which is neither a nystagmus nor a tremor. The eyes wander from side to side in a wide excursion which is interrupted at its extremity by a standstill period of varying duration. The mechanism of this movement, which is associated with blind eyes and with natural sleep, is not known, but Kestenbaum (1947) states that " it may be explained by irregular incidental central impulses meeting the gaze centres which are no longer controlled by the visual mechanism." Riley

appreciation of significant sounds is depressed. Cutaneous and deep sensibility is dulled and the threshold of stimulus necessary to initiate voluntary movement is raised. Voluntary movements, however, may still be performed in response to appropriate stimulus, but they are very slow and awkward. Thus, asynergia and inco-ordination develop, and when these effects are combined with the slurred speech and trunk ataxia characteristic of this level of anæsthetic depression and alcoholic intoxication, the whole suggests a failing synthesis of the proprioceptive impulses mediated by the neocerebellum and the flocculo-nodular lobes of the cerebellum. Pain sensibility is considerably dulled but cortical control is still adequate for rational behaviour; because of this, minor surgery may sometimes be performed at this level of anæsthetic depression, which is also called the stage of analgesia. At this level of anæsthetic depression it can be assumed that the functional activity of the remaining sensory association areas of the cerebral cortex, together with the neocerebellum and the flocculo-nodular lobes of the cerebellum, are depressd, but retain sufficient inhibitory control of the forebrain nuclei to ensure that a state of co-operative stupor exists.

With deepening anæsthesia, the subject then enters the stage of NON-COOPERATIVE STUPOR There is reason to believe, with the establishment of this level of anæsthesia, that the functional activity of the remaining areas of the cerebral cortex is completely depressed

During this period of anæsthesia, the appreciation of light touch, tactile localisation and discrimination and the ability to recognise intermediate degrees of temperature are progressively abolished. Ablation experiments indicate that these finer discriminatory sensory functions depend upon the functional activity of the cells of the post-central part of the parietal cortex, areas 3, 1 and 2, and it can be assumed that the cells of these areas of the cerebral cortex are completely depressed during this period of anæsthesia Accurate co-ordinate movement is no longer possible, for somatic sensory data normally available from areas 3, 1 and 2, and proprioceptive data from the neocerebellum and from the flocculo-nodular lobe of the cerebellum to the pre-central motor areas 4 and 6, are now considerably reduced, or completely lacking On this account, as also because the cells of area 4 are gradually

There is considerable autonomic representation in the cerebral cortex, and it is to be found mainly in the motor areas of the cortex. Thus, stimulation of certain discrete foci in area 8 produces dilatation of the pupil, a sympathetic reaction, while the stimulation of other discrete foci in this area produces lacrimation, a parasympathetic reaction. Para-sympathetic constriction of the pupil has been obtained by the stimulation of foci in area 19. In areas 4 and 6, separate foci are to be found, the stimulation of which results on the one hand in sympathetic effects such as an increase of pulse rate, an elevation of blood pressure, peripheral vaso-constriction and pilomotor effects, and, on the other, in para-sympathetic effects such as a decreased pulse rate, a fall of blood pressure, peripheral vasodilatation, excessive salivation and evacuation of the bladder. It is clear that there is extensive sympathetic and para-sympathetic representation at the cortical level; and, as the anæsthetic depression of the various areas of functional activity of the cerebral cortex proceeds, autonomic effects occur which vary in character and intensity as the premedication and the environment of the subject.

Hence, as anæsthesia deepens and the stage of co-operative stupor gives place to the stage of non-cooperative stupor, there is reason to believe that the functional activity of the *cells of the cerebral cortex* are completely depressed.[1] The various entities of cortical function are so interdependent upon one another that it is impossible to determine accurately the sequence of their individual depression during blood-borne anæsthesia, but memory is the first and hearing is probably the last cortical function to be abolished. It is probable that the cortical association areas are depressed soon after memory has been abolished, then the cortical areas responsible for vision, sensation, voluntary movement and, finally, hearing. The clinical condition of an adequately premedicated subject who has been successfully protected from external stimulus throughout simulates that of natural sleep for breathing is quiet and regular and salivary and bronchial secretions are normal in

[1] The anæsthetic depression of living cells has been defined as the freely reversible depression of the autonomic activity of cells Evidence has been advanced to suggest that this state is produced when the carbohydrate metabolism of a cell has been reduced solely to that provided by the metabolism of succinate, which, it is inferred, is the minimal carbohydrate metabolism compatible with the continued life of the cell.

(1930) states that " diseases of known extrapyramidal origin, particularly those attributed to strial pathological changes, are characterised by deviation from the normal in the realm of occulomotor control in regard to tonal changes and to the production of involuntary (eye) movements." There is no evidence of strial involvement at this level of anæsthesia, but the worm-like movement of the eyes can be looked upon as an extrapyramidal release-effect consequent upon the depression of the cells of areas 6, 8 and 9 of the cerebral cortex. The disturbance of spatial orientation and visual images is accompanied by loss of visual memory, object vision and light perception; optically elicitated eye movements are absent, but consensual pupillary reaction to light is still present. It can be assumed that the cells of the frontal eye field, area 8, the visual association areas 18 and 19, and the area striata of the calcarine cortex, area 17, are completely depressed at this level of anæsthetic depression.

At this level of anæsthetic depression, too, tinnitus and auditory hallucinations may occur. Auditory localisation and memory of auditory impressions begin to fail and there is a disturbance in the interpretation of significant sounds and spoken language, but the subject is not deaf Bi-lateral ablation of the temporal lobes has not to date been observed in Man, but auditory disturbances are most frequent in temporal lobe lesions. Unilateral ablation of the temporal lobe does not cause deafness in Man, but left-sided lesions in this area produce loss of memory of sounds, loss of the appreciation of significant sounds and loss of auditory localisation. It can be asumed that the functional activity of the cells of the temporal cortex are depressed during the stage of non-cooperative stupor; but it has often been observed in clinical anæsthetic practice that the sense of hearing persists after smell, taste, touch, and sight have been completely abolished.

The integration of articulate speech depends upon the integrity of the auditory and other afferent mechanisms, upon the synthesis of these afferent impressions and upon the skilled use of the muscles of respiration and articulation. And it is to be expected, as the association and sensory cortical areas become progressively depressed that speech will become slurred and then inarticulate, and will finally cease when area 4 is completely depressed and voluntary movement is consequently abolished.

pathetic components which are basically antagonistic but which interact harmoniously in normal conditions of life to maintain the internal environment within physiological limits. When both cerebral hemispheres are removed in an experimental animal, Bard (1928) and Cannon (1929) have shown that periodic discharges, which they term " sham rage," occur spontaneously or on stimulation. These outbursts of somatic and autonomic activity are predominantly sympathetic in character, for while the parasympathetic system tends to discharge discretely, the sympathetic system is more likely to discharge *en masse*. The effects observed when excitement occurs during the non-cooperative stupor stage of blood-borne anæsthesia stimulate the sham rage produced by Bard and Cannon so closely that it may be assumed that they are produced by the release of the hypothalamus from cortical control at this level of anæsthetic depression. The natural tendency for sympathetic overaction in a decorticated subject is accentuated during blood-borne anæsthesia, for atropine (or the allied drug, scopolamine) is invariably used, in doses which neutralise parasympathetic effects, as a pre-anæsthetic medicant in clinical anæsthetic practice.

This conclusion is strengthened for, as anæsthesia deepens, however violent the stage of non-cooperative stupor may have been, the subject passes abruptly to the stage of anæsthetic sleep, and the cessation of somatic and sympathetic effects with the onset of anæsthetic sleep is as striking and dramatic as it is abrupt. Thus, with the onset of anæsthetic sleep, breathing abruptly assumes a regular rhythm, and violent movement patterns cease: the pupils become small and no longer dilate reflexly to nociceptive stimuli, cardiac arrythmias and extrasystoles cease, and the pulse rate and the blood pressure rapidly return to normal limits.

Reflex dilatation of the pupils depend upon the integrity of the posterior and lateral hypothalamic nuclei. Bard observed that sham rage in a decorticated animal ceased when the posterior hypothalamic area was ablated and this observation was confirmed by Beattie, Brow and Long (1930). These observers found, moreover, that the cardiac arrythmias and extrasystoles observed electrocardiographically, which occurred spontaneously or on afferent stimulation during sham rage and in lightly chloroformed animals, ceased when the posterior hypothalamus was ablated. This is

volume; voluntary movement is not possible and skeletal muscles are flaccid but, on passive movement, resistance is encountered—at first intense, but diminishing if passive movement is continued; autonomic reactions are absent, or are so slight as to pass undetected; the pulse is regular, its rate is slightly increased, and the blood pressure is within normal limits. The blind stuporose subject is not conscious, but has not reached the stage of anæsthetic sleep, for his behaviour, when stimulated, is the very antithesis of the onset of natural sleep.

If external stimulus is permitted to act at this level of anæsthetic depression in an unpremedicated subject, intense excitement occurs and even in an adequately premedicated subject, reflex excitement ranging in intensity from restlessness to violent delirium may follow trivial degrees of emotional and/or physical stress, and may occur even without obvious cause. With the anæsthetic depression of the cerebral cortex, the subject retains only the grosser discriminatory aspects of sensation, but he reacts to nociceptive stimulus, to gross degrees of movement and, perhaps, to extremes of temperature. Freed from cortical control, his response to such stimuli is excessive and exaggerated; extravagant movement patterns, which are usually flexor in character, follow nociceptive and emotional stimuli and may be so violent as to require manual restraint. Breathing may assume any imaginable rhythm; lacrimal, salivary, and bronchial secretions may be excessive; vomiting, coughing, gagging, and even bronchospasm may occur; object vision is absent, the pupils which constrict reflexly to light are widely dilated, and there is a coarse worm-like lateral movement of the eyes; cutaneous vasodilatation causes flushing, and the subject may sweat profusely; the nose may bleed, a full bladder may empty and passive erection of the penis may occur; the pulse is rapid, the blood pressure rises and cardiac arrythmias and extrasystoles often occur. This response to external stimulus is characteristic of a decorticated subject, and the excessive and exaggerated character of these mixed autonomic and somatic effects indicates material overaction of the hypothalamus following its release from cortical control, for it is in the hypothalamus that such highly organised visceral and somatic reaction patterns are integrated.

The hypothalamus contains both sympathetic and parasym-

fail to dilate reflexly, the lateral worm-like movement of the eyes becomes slower and the length of its lateral excursion shortens; lacrimal, salivary and bronchial secretion diminish in volume, and the subject's condition stimulates that of peaceful light natural sleep. At this level of anæsthetic depression, however, appropriate stimulus produces alteration in the rhythm of breathing, and may result in excessive lacrimal, salivary and bronchial secretion; bronchial constriction may also occur; the pupils constrict reflexly to bright light; cutaneous vasodilatation and sweating may occur and, in the absence of adequate atropinization, the auriculo-ventricular conduction time is increased, the heart slows and the blood pressure falls; peristalsis of the stomach and the intestines may be increased; reflexes may be elicited and there is often an extensor rigidity of the legs and trunk which indicates that Dieter's nucleus is functionally active. These results of stimulation indicate that the parasympathetic entities of the hypothalamus are functionally active and that the thalamic nuclei are still able to receive and mediate afferent impulses during the stage of light anæsthetic sleep.

The anterior and middle nuclear masses of the hypothalamus are predominantly para-sympathetic entities. All the hypothalamic nuceli have copious intra-diencephalic connections. In general the anterior nuclei project to the middle and posterior nuclear masses, which also have connections with the cerebral cortex, the thalamus, the corpus striatum, the medulla, and the spinal cord. There is a growing mass of evidence which indicates that electrical or chemical stimulation of the anterior and middle hypothalamic nuclei produces para-sympathetic effects such as bladder contraction, increased gastric and intestinal peristalsis, cardiac slowing, and vasodilatation In general these effects simulate those produced when appropriate stimuli are permitted to act during light anæsthetic sleep. But, as anæsthesia deepens, the threshold of stimulus necessary to initiate these vegitative reactions gradually increases until, when at length the level of anæsthesia coincides with that of deep natural sleep, para-sympathetic effects cease and external stimulation no longer produces any appreciable autonomic response. This indicates that the *anterior and middle nuclear masses of the hypothalamus* are now depressed. It is significant, too, that at this level of deep anæsthetic sleep the heat-regulating mechanism

positive evidence that sympathetic overaction in a decorticated subject is initiated in the posterior and lateral hypothalamic nuclei. It strengthens the view that reflex excitement during the non-cooperative stupor stage of blood-borne anæsthesia results from the release of the hypothalamus from cortical control, and indicates that the cessation of sympathetic overaction—and particularly of cardiac arrythmias results from the anæsthetic depression of the *posterior and lateral hypothalamic nuclei.*

It is more than a coincidence that the onset of anæsthetic sleep occurs at the same time as the abrupt cessation of sympathetic overaction. The phenomenon of sleep is nowadays associated with the posterior hypothalamus and the mammillary bodies. In encephalitis lethargica, the hypothalamus is involved more often than any other region of the central nervous system except the substantia nigra. Lesions in the region of the posterior hypothalamus and the mammillary bodies produce a state of somnolence which often progresses to a state of continuous sleep, and the destruction of the mammillary bodies in cats and monkeys has been shown to produce somnolence. Bailey (1938) observed that " no part of the brain is so prone to cause loss of consciousness if handled than the posterior hypothalamus and the grey matter of the aqueduct of Sylvius." On the other hand, stimulation of a wide area of the hypothalamus, and not destruction of tissue, was believed by Hess (1932) to cause a state of sleep. In such experimental somnolent states, respiration is slow, the pupils are small and react to light, there is a slight fall of body temperature, a diminished pulse rate, and a fall of blood pressure, and these are some of the signs of natural sleep. And it is most significant that in anæsthesia the sudden cessation of sympathetic overaction produced by the anæsthetic depression of the posterior and lateral hypothalamus is accompanied by the coincident onset of anæsthetic sleep. This suggests that the stage of non-cooperative stupor ends and the stage of anæsthetic sleep begins when *the posterior and lateral hypothalamic nuclei and probably the mammillary bodies* are completely depressed.

The onset of ANÆSTHETIC SLEEP is characterised by regular breathing which is more rapid than normal, and by the fall of the pulse rate and blood pressure to normal limits. Movement patterns cease and skeletal muscles are flaccid; the pupils are small and

fail to dilate reflexly, the lateral worm-like movement of the eyes becomes slower and the length of its lateral excursion shortens; lacrimal, salivary and bronchial secretion diminish in volume, and the subject's condition stimulates that of peaceful light natural sleep. At this level of anæsthetic depression, however, appropriate stimulus produces alteration in the rhythm of breathing, and may result in excessive lacrimal, salivary and bronchial secretion; bronchial constriction may also occur; the pupils constrict reflexly to bright light; cutaneous vasodilatation and sweating may occur and, in the absence of adequate atropinization, the auriculo-ventricular conduction time is increased, the heart slows and the blood pressure falls; peristalsis of the stomach and the intestines may be increased; reflexes may be elicited and there is often an extensor rigidity of the legs and trunk which indicates that Dieter's nucleus is functionally active. These results of stimulation indicate that the parasympathetic entities of the hypothalamus are functionally active and that the thalamic nuclei are still able to receive and mediate afferent impulses during the stage of light anæsthetic sleep.

The anterior and middle nuclear masses of the hypothalamus are predominantly para-sympathetic entities. All the hypothalamic nuceli have copious intra-diencephalic connections. In general the anterior nuclei project to the middle and posterior nuclear masses, which also have connections with the cerebral cortex, the thalamus, the corpus striatum, the medulla, and the spinal cord. There is a growing mass of evidence which indicates that electrical or chemical stimulation of the anterior and middle hypothalamic nuclei produces para-sympathetic effects such as bladder contraction, increased gastric and intestinal peristalsis, cardiac slowing, and vasodilatation In general these effects simulate those produced when appropriate stimuli are permitted to act during light anæsthetic sleep. But, as anæsthesia deepens, the threshold of stimulus necessary to initiate these vegitative reactions gradually increases until, when at length the level of anæsthesia coincides with that of deep natural sleep, para-sympathetic effects cease and external stimulation no longer produces any appreciable autonomic response. This indicates that the *anterior and middle nuclear masses of the hypothalamus* are now depressed. It is significant, too, that at this level of deep anæsthetic sleep the heat-regulating mechanism

of the body fails and the subject becomes poikilothermic in character.

Barbour (1921), Keller and Hare (1932) and others have shown that the heat-regulating mechanism of the body fails when the hypothalamus is destroyed and that it is adequate as long as the functional activity of the hypothalamus is intact. The mechanism of heat preservation consists of shivering, the mobilization of carbohydrate reserves, vasoconstriction, piloerection, increase in the heart rate and elevation of the metabolic rate It is thus a sympathetic response, for all these reactions, except shivering, are produced by adrenaline Heat loss on the other hand is a para-sympathetic response and consists of sweating, vasodilatation and increased breathing. The regulation of heat loss is to be found in the anterior and middle hypothalamic nuclear masses, particularly the tuber nuclei. Davison and Selby (1935) reported persistent hyperthermia in a man with a small lesion which involved the tuber nuclei of the hypothalamus. Lesions in the posterior hypothalamus invariably produce hypothermia. Antipyretic drugs produce heat loss by their ability to depress the anterior and posterior hypothalamic nuclei, and thus release the middle nuclear masses of the hypothalamus. The mechanism of heat regulation undoubtedly resides in the hypothalamus and depends upon the interaction of the sympathetic and parasympathetic components of this basal nucleus. During di-ethyl ether anæsthesia, the anæsthetic depression of the posterior and lateral hypothalamic nuclei with the onset of anæsthetic sleep abolishes heat preservation, and this is soon followed by the inability to regulate heat loss when the anterior and middle hypothalamic nuclei are depressed during deep anæsthetic sleep And the depression of the functional activity of the hypothalamus is consistent with the poikilothermic state of the subject during deep anæsthetic sleep (c f. page 31)

When the stage of DEEP ANÆSTHETIC SLEEP has been attained, the signs of anæsthesia indicate that the *cerebral cortex* and the *hypothalamus* have been completely depressed The subject is now poikilothermic and, although cardiovascular effects of a minor character may follow appropriate stimuli, autonomic reactions, which are now integrated at the medullary level, practically cease The somatic system of the subject still, however, reacts in a reflex

manner to external stimuli of adequate intensity. The pupils constrict sluggishly when exposed to bright light, and the lateral worm-like movement of the eyes is very slow or has ceased. Vocalization and alterations of the rhythm of breathing may result from potent stimuli: reflexes such as the corneal reflex, the patella reflex, etc., react sluggishly to their appropriate stimulus, and tonic reflexes can be elicited, for flaccid skeletal muscles become rigid when local and/or peritoneal stimulation occurs. The righting reflexes in the blind thalamic subject during deep anæsthetic sleep suggests that exteroceptive and proprioceptive impulses from the head, neck, trunk and limbs are now insufficiently integrated by the thalamus and vestibular nucleus to activate their appropriate righting reflex.

As anæsthesia deepens, the subject soon passes from the stage of deep anæsthetic sleep to the level of anæsthetic depression, which in this discussion has been termed the stage of COMPLETE SENSORY LOSS This can be looked upon as the terminal event in the anæsthetic depression of *the areas of sensory co-ordination of the brain* and it results in a loss of the ability to react in a reflex manner to all except the most intense forms of proprioceptive stimuli. The stage of complete sensory loss thus coincides with Guedel's second plane of surgical anæsthesia.

Sensory limens alter early in anæsthesia, and the evidence which has been discussed indicates that the ability of the central nervous system to integrate sensory impulses is progressively depressed during anæsthetic induction to the level of deep anæsthetic sleep.

When memory has been abolished and the stage of co-operative stupor has been attained, the subject is analgesic. Tactile localisation, and discrimination and the appreciation of intermediate degrees of temperature, are dulled and the threshold stimulus is raised to a degree which permits minor surgery to be performed. The subject reacts sluggishly to cutaneous, deep and painful stimulus; and asynergia, inco-ordination and slurred speech are present. Visual memory is absent, the appreciation of bright light is present, but the worm-like movements of the eyes suggests that object vision has been abolished. Auditory localization is inaccurate, but the subject may react and even perform simple voluntary movements in response to terse, loud, simple words of command. These objective signs indicate that the threshold of stimulus necessary to activate the association and

sensory areas of the cerebral cortex, the neocerebellum and the flocculo-nodular lobe of the cerebellum is materially raised during the stage of co-operative stupor. This raised threshold stimulus is probably more apparent than real, for the essentially co-operative behaviour of the subject indicates that the inhibitory control normally exercised by the cerebral cortex on the forebrain nuclei through the cortico-thalamic fibres is intact, and that the absence of reaction to stimulus during the co-operative stupor stage is due, in part at least, to cortical inhibition.

With deepening anæsthesia, the subject then enters the stage of non-cooperative stupor. As the term implies, the response of the subject during this stage of anæsthesia is in marked contrast to the stage of co-operative stupor which precedes it, for when external stimulus is permitted to act, the subject's reactions indicate that he is now hypersensitive to stimulus. The violent movement patterns, and the excessive autonomic response which may occur, suggest that the inhibitory control exercised by the cerebral cortex over the forebrain nuclei is now abolished. All the subjective signs observed during this stage of anæsthesia indicate that the finer discriminatory aspects of sensation of this blind stuporose subject are now lost and that the synthesis of sensory impressions necessary for voluntary acts, such as articulate speech, is impossible. When these observations are coupled with the excessive and exaggerated response of the subject so characteristic of this stage of anæsthesia, it can be concluded that the sensory loss produced during the stage of non-cooperative stupor is identical with that of a decorticated subject. Like the forebrain preparation, the subject responds only to painful stimuli, to gross degrees of movement and perhaps to extremes of temperature; moreover, such stimuli often result in sham rage and complicated movement patterns, but voluntary movement is not possible.

The onset of anæsthetic sleep, characterised by the abrupt cessation of sympathetic overaction, has been attributed to the depression of the posterior and lateral hypothalamic nuclei and the mammillary bodies, and evidence has been discussed which indicates that this is followed early in anæsthetic sleep by the depression of the para-sympathetic entities of the hypothalamus. When the level of deep anæsthetic sleep has been established, autonomic effects are integrated principally at the medullary level:

the thalamus represents the highest sensory association nucleus and the corpus striatum represents the highest centre of motor control.

The THALAMUS, which is the principal sensory station of the forebrain, mediates afferent impulses from the somatic system. It projects to the cerebral cortex and receives cortico-inhibitory fibres from the cerebral cortex and it is intimately related to the nuclei of the corpus striatum. The thalamus consists of three groups of nuclei which are:

1. *The cortical relay nuclei*, which receive and mediate afferent impulses from the somatic system and from the special sense organs, consist of the ventral and anterior nuclear masses and the geniculate bodies. The lateroventral nuclei receive proprioceptive data from the cerebellum *via* the brachium conjunctivum. The posteroventral nuclei receive exteroceptive and proprioceptive data from the trigeminal nuclei, from the spinothalamic tract and from the posterior columns *via* the medial leminiscus. The geniculate bodies receive visual and auditory impressions from their respective receptors, and the anterior nuclear masses receive afferents from the mammillary bodies. In these nuclei spatial representation of sensation is sharply localised, as is also the case in the areas of the cerebral cortex to which they project. These nuclei also receive cortico-inhibitory fibres from the pre-frontal, the visual, the post-central and the pre-central areas of the cerebral cortex. When the cerebral cortex is ablated, the cortical relay nuclei of the thalamus degenerate almost completely.

2. The second group of thalamic nuclei are the *Association nuclei*, which consist of dorsomedial nuclei, the lateral nuclei, and the pulvinar. They project to the association areas of the cerebral cortex and have numerous connections with the nuclei of the forebrain, but receive no fibres from the ascending system. The large-celled part of the dorsomedial nucleus projects to the hypothalamus and its small-celled part to the pre-frontal areas of the cerebral cortex. Degeneration of this nucleus follows ablation of the pre-frontal areas (areas 9, 10 and 12). The principle connections of the lateral nuclei are with the ventral relay nuclei, and they project to the posterior parietal region of the cerebral cortex (areas 5 and 7). The pulvinar, which is associated with visual and auditory integration, projects to the peristriate region of the cerebral cortex (area 18) and to the auditory association area of

the posterior temporal region of the cerebral cortex (areas 18 and 22). The thalamic association nuclei degenerate almost completely when the cerebral cortex is ablated.

3. Finally there are the *sub-cortical group of thalamic nuclei*, whose connections are restricted to the nuclei of the forebrain, the thalamus, the hypothalamus, the sub-thalamus, and the corpus striatum. Little is known of their function and they are probably concerned with intradiencephalic association and with visceral function. When the cerebral cortex is removed, the sub-cortical thalamic nuclei are unaffected.

Since only the subcortical nuclei of the thalamus survive decortication, it can be assumed that the therapeutic decortication produced during the non-cooperative stupor stage of blood-borne anæsthesia materially affects the integrity of the association and the cortical relay nuclei of the thalamus. On the general assumption that the sequence of depression of thalamic nuclei follows the general order of depression of the discrete topographical areas of the cortex to which they project, and that the nuclei concerned with association are more specialized and consequently more susceptible, it might be expected that the functional activity of the dorsomedial association nuclei, which project to the prefrontal area of the cortex, is depressed early in the stage of non-cooperative stupor. And then in order, the visual entities of the pulvinar and the lateral geniculate bodies, the lateral association nuclei, and the posteroventral relay nuclei which project to the sensory areas, the lateroventral relay nuclei which project to the motor areas, and then the auditory entities of the pulvinar and the median geniculate bodies The complicated movement patterns which may occur during this stage of anæsthesia indicate that the ventral postero-medial and posterolateral relay nuclei—within which there is sharply localized spatial sensory representation of the head and neck, legs, arms and trunk—are still functionally active. With the onset of anæsthetic sleep, movement patterns cease The muscles of the head and neck, which are flaccid, fail to respond to external stimulus; this indicates that the ventral posteromedial thalamic nuclei are now depressed It is probable, at this level of anæsthesia, that the ventral posterolateral thalamic nuclei are still functionally active, for extensor rigidity of the legs and trunk may occur during light anæsthetic sleep; and this effect, which can

be regarded as a generalized intersegmental response modified at a higher level, is abolished during deep anæsthetic sleep, when, it is assumed, the ventral postero-lateral thalamic nuclei are at length depressed. Hence, when anæsthetic sleep has been established, there is reason to believe that the cerebral cortex, the hypothalamus and the cortical relay and association nuclei of the thalamus have been depressed; and at this level of anæsthetic depression it is observed that external stimulation now produces only a simple segmental reflex response. Protective reflexes, such as pupillary constriction, and the corneal and cough reflexes, react to appropriate stimulus; and segmental spinal reflexes such as the patella reflex, are elicited with difficulty. The righting reflexes are abolished but tonic rigidity in the muscles of the trunk is produced in response to local proprioceptive stimulus.

With the onset of the stage of COMPLETE SENSORY LOSS, *the subject fails to react in a reflex manner to all forms of external stimulation except intense degrees of proprioceptive stimulus.* For example, the rapid forceful dilatation of the anal sphincter, local stretching of large muscle groups, and pulling upon the peritoneum or the mesentery, produces intense rigidity of the trunk muscles. This is sometimes accompanied by an alteration in the rhythm of breathing, with or without vocalization and with perhaps a sharp rise of pulse rate and a slight rise of blood pressure which last for the duration of the stimulus. All other forms of stimulus likely to occur during an operative surgical procedure produce no reaction on the part of the subject. Nociceptive stimulus is without effect; the pupils no longer constrict when exposed to bright light; the eyeball is stationary in the central position; lacrimal, salivary, and bronchial secretions cease, the corneal, gag, vomit, and cough reflexes and all other forms of reflex movement are abolished. Tonic reflexes in all skeletal muscles except the large muscle groups of the trunk are inactive, and the most striking feature of this level of anæsthetic depression is the intense rigidity produced in the large muscles of the trunk when these muscles, and/or the peritoneum or mesentery, are stretched. In the absence of such proprioceptive stimuli, the response of the subject is similar to that of a bulbospinal preparation; and there is reason to believe, when anæsthesia to the level of complete sensory loss has been established, that the ability to integrate all sensory impulses, except

the posterior temporal region of the cerebral cortex (areas 18 and 22). The thalamic association nuclei degenerate almost completely when the cerebral cortex is ablated.

3. Finally there are the *sub-cortical group of thalamic nuclei*, whose connections are restricted to the nuclei of the forebrain, the thalamus, the hypothalamus, the sub-thalamus, and the corpus striatum. Little is known of their function and they are probably concerned with intradiencephalic association and with visceral function. When the cerebral cortex is removed, the sub-cortical thalamic nuclei are unaffected.

Since only the subcortical nuclei of the thalamus survive decortication, it can be assumed that the therapeutic decortication produced during the non-cooperative stupor stage of blood-borne anæsthesia materially affects the integrity of the association and the cortical relay nuclei of the thalamus. On the general assumption that the sequence of depression of thalamic nuclei follows the general order of depression of the discrete topographical areas of the cortex to which they project, and that the nuclei concerned with association are more specialized and consequently more susceptible, it might be expected that the functional activity of the dorsomedial association nuclei, which project to the prefrontal area of the cortex, is depressed early in the stage of non-cooperative stupor. And then in order, the visual entities of the pulvinar and the lateral geniculate bodies, the lateral association nuclei, and the *posteroventral relay nuclei which project to the sensory areas*, the lateroventral relay nuclei which project to the motor areas, and then the auditory entities of the pulvinar and the median geniculate bodies. The complicated movement patterns which may occur during this stage of anæsthesia indicate that the ventral posteromedial and posterolateral relay nuclei—within which there is sharply localized spatial sensory representation of the head and neck, legs, arms and trunk—are still functionally active. With the onset of anæsthetic sleep, movement patterns cease. The muscles of the head and neck, which are flaccid, fail to respond to external stimulus; this indicates that the ventral posteromedial thalamic nuclei are now depressed. It is probable, at this level of anæsthesia, that the ventral posterolateral thalamic nuclei are still functionally active, for extensor rigidity of the legs and trunk may occur during light anæsthetic sleep; and this effect, which can

the nuclei of the extrinsic muscles of the eyes has ceased. This in turn suggests, when deep anæsthetic sleep has been attained, that other cranial motor nuclei also lack impulses normally projected to them from the globus pallidus; since, at this level of anæsthetic depression, they integrate only reflexes of a simple segmental type, it can be assumed that this is, in fact, the case. When at length anæsthesia to the level of complete sensory loss has been achieved, rigidity of the trunk muscles is the only response elicited, and it can be inferred that the *cranial sensory nuclei* are themselves now depressed, and it is of value to consider the response of some of the simple segmental reflexes which are employed in clinical practice at this level of anæsthesia.

Afferent impulses concerned with the light reflex pass in the optic tract to the tectal region, and a second order of the neurons projects from thence to the Edinger-Westphal division of the occulomotor nucleus from which effector neurons originate and pass in the occulomotor nerve to the constrictor of the pupils. And the inability of the pupils to constrict in response to bright light indicates that the tectal region is depressed at the stage of sensory loss, but it is probable that the absence of sensory data from the globus pallidus to the Edinger-Westphal nuclei is also a contributing factor, and this motor nucleus may even be depressed at this level of anæsthesia.

The arrest of the worm-like lateral movement of the eyes during deep anæsthetic sleep indicates that extrapyramidal interference has ceased. The complete inability to elicit eye movements during the stage of sensory loss suggests that afferent impulses to the motor nuclei of the extrinsic muscles of the eye are absent, and/or that these nuclei are themselves depressed at this stage of anæsthesia It is probable that the afferent side of the reflex arc is completely depressed, but the absolute inability to produce eye movements or elevation of the upper eyelids during the stage of complete sensory loss—even with the intense stimulation produced by the passage of electric current through the frontal region of the skull during electrical convulsive therapy—indicates that these motor nuclei themselves are also depressed during the stage of complete sensory loss. The paralysed extrinsic muscles of the eyes are in balance and the eyes assume the central position. And it is probable that the occulomotor, Edinger-Westphal's, the trochlear,

those responsible for motor tone in the trunk muscles, is abolished at a supra-medullary level. This must result in a material diminution of the sensory data normally projected to the basal ganglia which have no direct communication with the cerebral cortex or with the spinal cord.

The BASAL GANGLIA consist of the neostriatum, the caudate nucleus and the putamen, and the paleostriatum, the globus pallidus. The *caudate nucleus* and the *putamen* are primarily intradiencephalic association centres and they are histologically identical. The *globus pallidus*, which has retained its primitive rôle, is a motor nucleus. The caudate nucleus receives projections from the medial nuclei of the thalamus, but has no connections with the brain stem nuclei or with the spinal cord, and it projects to the putamen and the globus pallidus. The putamen receives no projections from the thalamus but many from the caudate nucleus, and it projects to the globus pallidus. The globus pallidus receives fibres from the parietal cortex and extensive afferent fibres from the forebrain nuclei, but its main afferent projections come from the caudate nucleus and the putamen. It also receives projections from the centromedial subcortical thalamic nuclei, for these nuclear masses degenerate when the globus pallidus is damaged, which suggests that the subcortical thalamic nuclei have important striatal connections. Both anatomically and phylogenetically the globus pallidus and the substantia nigra are linked, and it has been observed that the one is seldom involved without the other. Since both the pyramidal and extrapyramidal representations in the cerebral cortex are depressed, the globus pallidus is now the principle motor nucleus of the subject, and it projects through the ansa lenticularis to the substantia nigra, to the subthalamic nucleus of Luy's, to the red nucleus and to the motor nuclei of the cranial nerves, viz. the occulo-motor, and Edinger-Westphal's nuclei, the trochlear, abducens, facial, hypoglossal, and the nucleus ambiguus.

With the depression of the cortical relay and association nuclei of the thalamus during anæsthetic sleep, sensory data normally projected to the neostriatum and the globus pallidus are materially reduced, and the slowing and ultimate arrest of the lateral worm-like movement of the eyes during deep anæsthetic sleep indicates that at this level of anæsthesia extrapyramidal interference with

the subcortical thalamic nuclei, the neostriatum, all the cranial sensory nuclei, and the motor nuclei of the extrinsic muscles of the eyes, are depressed when the stage of complete sensory loss has been attained. At this level of anæsthetic depression, the subject breathes regularly and automatically and his pulse rate and his blood pressure are maintained within normal limits, for he reacts through his chemoreceptors and medullary nuclei to changes in his internal environment, his blood. Except that local stretching produces local rigidity in the skeletal muscles of the trunk, he fails to react in a reflex manner to other than intense proprioceptive stimulus. At the stage of complete sensory loss, therefore, the two dangerous and unpredictable variables—the subject's reaction to *emotion and external stimulus*—have been eliminated. The importance of this fact cannot be overstressed. With the elimination of these two variables the subject enters a zone of safety for the first time since anæsthesia commenced, and this zone of safety continues until at length, with deepening anæsthesia, the vital medullary centres are depressed.

With deepening anæsthesia, the skeletal muscles of the trunk now become flaccid, even in the presence of intense proprioceptive stimulation, and this muscular relaxation, as it is termed clinically, is first manifest in large muscle groups of the trunk and then in the intercostal muscles and the sternocostal part of the diaphragm. When intercostal paralysis has been produced, this is the deepest level of anæsthetic depression *desired or required* in clinical anæsthetic practice, and at this level the subject is, in effect, a bulbo-spinal preparation. Like the decerebrate animal, he reacts to changes in his internal environment, but differs in not reacting in a reflex manner to external stimulation; and he does not exhibit the intense rigidity characteristic of the decerebrate animal. A recapitulation of the alterations in movement and muscle tone which occur during anæsthetic induction to the level of complete sensory loss permits certain inferences to be made which serve as a starting point in a discussion of the mode of production of muscular relaxation during blood-borne anæsthesia.

During the stage of non-cooperative stupor, skeletal muscles are spastic with lengthening and shortening reactions. Spasticity is an extrapyramidal cortical release phenomenon and, in this instance, can be attributed to the depression of the cerebral cortex

and the abducens nuclei are depressed at the stage of complete sensory loss.

The corneal reflex is mediated on its sensory side by the fibres of the trigeminal nerve, while its efferent fibres emerge in the fibres of the facial nerve. At the stage of complete sensory loss, stimulation of the whole receptive field of the trigeminal nerve, viz. the face and scalp, the nasal passages and sinuses and the anterior two-thirds of the tongue, *fails to produce a somatic or an autonomic* response; and the motor nuclei of the facial nerve, lacking impulses from this source as also from the globus pallidus, fail to activate the orbicularis palpebrarum. It is significant that the efferent fibres of this reflex arc, the fibres of the facial nerve, are functionally active during the stage of complete sensory loss, for, when during continuous electrical narcosis the terminals are placed low on each temporal area of the skull, at this level of anæsthesia a typical snarl, with showing of the teeth, is invariably present.

At this level of anæsthesia, too, lacrimal, salivary, and bronchial secretions cease, and the gag and cough reflex is abolished. Stimulation of the whole field of the affector side of the reflex arc responsible for these secretions and reflexes, consisting of the area served by the trigeminal nerve together with that served by the glossopharyngeal nerve, viz. the whole of the nasopharynx, the posterior pharyngeal wall, and the posterior one-third of the tongue, is now ineffective. In each instance the effector organ responsible for these secretions is functionally active, for if atropine has been omitted as a pre-anæsthetic medicant, prostigmine in appropriate dosage produces tears, saliva, and bronchial secretions at the stage of complete sensory loss. And it can be concluded that the sensory nuclei of the trigeminal and glossopharyngeal nerves are depressed at the stage of complete sensory loss

Auditory stimulus now produces no response whatsoever, and this implies that, in addition to the median geniculate bodies, the ventral and dorsal auditory nuclei are now completely depressed Visual entities failed during the stage of non-cooperative stupor, and the vestibular nuclei ceased to integrate the righting reflexes during the stage of anæsthetic sleep.

And there is reason to believe that *the cerebral cortex, the hypothalamus, the cortical relay and assocation nuclei and perhaps,*

these muscles are abolished. They fail to react to nociceptive or proprioceptive stimulus and are quite relaxed. At this level of anæsthetic depression, the large muscle groups of the trunk are flaccid even when exposed to nociceptive stimulus, but local proprioceptive stimulus produces local rigidity in extensors and flexors alike. Owing to the general adoption of the supine position during surgical procedures, flexor rigidity of the abdominal muscles is commonly manifest at this level of anæsthesia, but in the lateral position, as for a nephrectomy, extensor rigidity of the trunk muscles may be observed during anæsthesia to the level of complete sensory loss. This rigidity, which is reflex in origin, is produced by proprioceptive impulses in the muscles themselves, and it can be abolished by the intramuscular injection of local anæsthetics. Grinker (1937) believes that the thalamus and the neostriatum exercises an inhibitory effect upon the globus pallidus and this reflex rigidity may be attributed to the release of the globus pallidus consequent upon the anæsthetic depression of the nuclei of the thalamus and the neostriatum at this stage of anæsthesia.

The abolition of muscle tone in the muscles of the trunk during blood-borne anæsthesia can be looked upon as the terminal event in the anæsthetic depression of the areas of motor co-ordination of the brain. It is produced by the failure, at a supramedullary level, of cranial motor nuclei to integrate proprioceptive data and so reinforce the segmental reflex responsible for this rigidity. When the stage of complete sensory loss has been achieved, the body reacts only to proprioceptive stimulus, and it has been concluded that the globus pallidus is functionally active at this level of anæsthesia. Loss of muscle tone in the muscles of the trunk, as anæsthesia deepens beyond the level of complete sensory loss, can be attributed to the anæsthetic depression of the globus pallidus, followed by the successive depression of the motor nuclei of the pons and the brain stem.

Sherrington and others have shown in experimental animals that brain section which excludes the large celled caudal part of the red nucleus from the brain stem produces decerebrate rigidity. Muscle tone is markedly increased and rigidity is most intense in the extensor muscles opposing gravity. This increase of muscle tone is a reflex act which is not dependent upon afferent skin stimula-

which has been seen to occur at this level of anæsthesia. And the view that cortical control is inhibited at the level of non-cooperative stupor is strengthened by the excessive and exaggerated nature of the purposeful movement patterns which follow emotional and/or physical stress. If the emotional factor is avoided during anæsthetic induction, external stimulation in the late stage of non-cooperative stupor, or in the early stage of anæsthetic sleep, no longer produces generalised movement patterns; but reflexes of a segmental nature, such as the patella reflex, are exaggerated, and generalised extensor rigidity of the legs and trunk may occur. This extensor rigidity is such that the subject can often be moved in one piece, like a statue, and it may make *it impossible to place the subject in the lithotomy position.* Such positive supporting reactions are present in decerebellate monkeys, and this generalised extensor rigidity suggests that cortical and cerebellar control is now abolished, that groups of stretch reflexes reinforced by positive supporting reactions which arise in the otolith organs are active, and that Dieter's nucleus, the lateral vestibular nucleus, is functionally active.

With the establishment of anæsthetic sleep, extensor rigidity abruptly ceases, and postural reflexes are abolished. All the righting reflexes, the optic, the head, the neck, the trunk, and the labyrinth righting reflex are now inactive. At this level of anæsthesia, stretching of skeletal muscles and/or nociceptive stimulus as, *for example, to the toes during the operation for the removal* of a toenail, results in a flexor response. Moreover, during anæsthetic sleep, when continuous electrical stimulation is passed through the skull, as during the continuous electrical narcosis employed in the treatment of certain psychiatric subjects, the arms are adducted at the shoulders, the elbows are semi-flexed, the forearms are pronated, the wrists and fingers are flexed, and the legs are extended And this posture suggests that during the stage of anæsthetic sleep the globus pallidus and Dieter's nucleus are functionally active, but that these nuclei receive insufficient exteroceptive and proprioceptive data to activate them.

As deep anæsthetic sleep merges into the stage of complete sensory loss, small muscle groups, such as the extrinsic muscles of the eye, lose their resting tone. Then the muscles of the extremities become flaccid, and lengthening and shortening reactions in

these muscles are abolished. They fail to react to nociceptive or proprioceptive stimulus and are quite relaxed. At this level of anæsthetic depression, the large muscle groups of the trunk are flaccid even when exposed to nociceptive stimulus, but local proprioceptive stimulus produces local rigidity in extensors and flexors alike. Owing to the general adoption of the supine position during surgical procedures, flexor rigidity of the abdominal muscles is commonly manifest at this level of anæsthesia, but in the lateral position, as for a nephrectomy, extensor rigidity of the trunk muscles may be observed during anæsthesia to the level of complete sensory loss. This rigidity, which is reflex in origin, is produced by proprioceptive impulses in the muscles themselves, and it can be abolished by the intramuscular injection of local anæsthetics. Grinker (1937) believes that the thalamus and the neostriatum exercises an inhibitory effect upon the globus pallidus and this reflex rigidity may be attributed to the release of the globus pallidus consequent upon the anæsthetic depression of the nuclei of the thalamus and the neostriatum at this stage of anæsthesia.

The abolition of muscle tone in the muscles of the trunk during blood-borne anæsthesia can be looked upon as the terminal event in the anæsthetic depression of the areas of motor co-ordination of the brain. It is produced by the failure, at a supramedullary level, of cranial motor nuclei to integrate proprioceptive data and so reinforce the segmental reflex responsible for this rigidity. When the stage of complete sensory loss has been achieved, the body reacts only to proprioceptive stimulus, and it has been concluded that the globus pallidus is functionally active at this level of anæsthesia. Loss of muscle tone in the muscles of the trunk, as anæsthesia deepens beyond the level of complete sensory loss, can be attributed to the anæsthetic depression of the globus pallidus, followed by the successive depression of the motor nuclei of the pons and the brain stem.

Sherrington and others have shown in experimental animals that brain section which excludes the large celled caudal part of the red nucleus from the brain stem produces decerebrate rigidity. Muscle tone is markedly increased and rigidity is most intense in the extensor muscles opposing gravity. This increase of muscle tone is a reflex act which is not dependent upon afferent skin stimula-

tion. It is abolished when the relevant posterior nerve roots are severed or when procaine is injected into the rigid muscle, and it is initiated by proprioceptive impulses produced in the muscles themselves. The intensity of decerebrate rigidity is progressively increased as the plane of section of the brain stem moves caudally; when at length Dieter's nucleus (the lateral vestibular nucleus) is excluded, decerebrate rigidity is abolished. Decerebrate rigidity is thus a proprioceptive reflex and the integrity of Dieter's nucleus, which contains large motor cells and is the origin of the vestibulo-spinal tract, is indispensable to this reflex act. It can be looked upon as a release mechanism which first appears when the caudal part of the red nucleus is destroyed and it increases in intensity as the motor nuclei of the pons and brain stem are successively destroyed until, at length, when the lateral vestibular nucleus is destroyed, proprioceptive data are no longer integrated in the central nervous system at a supramedullary level and complete flaccidity occurs in all skeletal muscles.

Muscular rigidity in a decerebrate animal can be abolished in five ways:

(1) The initiation of proprioceptive impulses can be prevented at their source in the muscles themselves by the intramuscular injection of an effective solution of local anæsthetic. (2) The transmission of proprioceptive impulses to the central nervous system may be arrested by section or blocking of the relevant posterior nerve roots or ascending tracts. (3) The integration of proprioceptive impulses can be prevented by the destruction or depression of Dieter's nucleus. (4) The relevant descending tracts, or the anterior nerve roots concerned, may be depressed or destroyed. And finally (5) motor impulses which reach the neuromuscular junction may be blocked by an agent such as d-tubocurarine chloride. It is significant that anæsthesia to the level of complete sensory loss abolishes in a reversible manner the rigidity of a decerebrate animal. Blood-borne anæsthesia to the level of complete sensory loss does not, however, prevent the initiation of proprioceptive impulses in skeletal muscles, and its concentration is below the threshold necessary to depress nerve fibres. It follows that blood-borne anæsthetics in concentrations necessary to produce complete sensory loss do not interfere with the ability of the decerebrate animal to initiate or transmit proprioceptive impulses, and the

abolition of decerebrate rigidity at the level of complete sensory loss can be attributed to the anæsthetic depression of Dieter's nucleus, and/or to the blocking of these impulses to the rigid muscle at the neuromuscular junction.

Decerebrate rigidity has no parallel in blood-borne anæsthesia; and during the period of anæsthesia which extends from the stage of complete sensory loss until bulbospinal status has been achieved, skeletal muscles are flaccid in the absence of proprioceptive stimulus, and there is evidence that the functional activity of Dieter's nucleus is depressed during the stage of complete sensory loss. When proprioceptive stimulus is permitted during the stage of complete sensory loss, only the trunk muscles become rigid; this rigidity, which is intense, is attributed to an inter-segmental spinal reflex reinforced at a higher level by the globus pallidus, the pontine and the brain stem nuclei, following their release from the inhibiting action of the thalamus and the neostriatum. As anæsthesia deepens, the trunk muscles gradually relax until when bulbospinal status has been at length achieved, all the trunk muscles except the crural fibres of the diaphragm are toneless, even in the presence of intense proprioceptive stimulus. This effect may be attributed to the successive depression of the globus pallidus, the pontine and, finally, the brain stem motor nuclei, for as reinforcement of the intersegmental reflex from the higher level becomes less intense, muscle tone progressively diminishes. And there is evidence that the intensity of motor impulses reaching the neuromuscular junction of the skeletal muscles of the trunk *is considerably reduced during the stage of complete sensory loss.*

The amount of d-tubo-curarine chloride which must be injected intravenously to produce curarisation of the muscles of the trunk can be taken as a measure of the quantum of acetylcholine (ACh) present at the neuromuscular junction of these muscles, and this, in turn, is a measure of the intensity of the barrage of motor nerve impulses which reach this site and so effect the release of this quantum of acetylcholine. In conscious or lightly anæsthetised subjects weighing about 70 kilos, it is observed that the intravenous injection of 30 milligrams of d-tubo-curarine chloride produces absolute loss of muscle tone in the muscles of the trunk, while an identical result is produced after the intravenous injection of 10 milligrams of d-tubo-curarine chloride in a subject of com-

parable size anæsthetised to the level of complete sensory loss. This result indicates that the quantum of acetylcholine released at the neuromuscular junction of the muscles of the trunk during the stage of complete sensory loss *is considerably smaller* than in a conscious or lightly anæsthetised subject, and this infers that *the intensity of the barrage of motor nerve impulses which reach the neuromuscular junction of these muscles during the stage of complete sensory loss is materially smaller than occurs in a conscious or lightly anæsthetised subject.* Moreover, if anæsthesia is maintained at the level of complete sensory loss, this original injection of 10 milligrams of d-tubo-curarine chloride will continue to produce full curarisation for three to five hours even in the presence of intense proprioceptive stimulation. This infers that the release of acetylcholine during the stage of complete sensory loss is so curtailed that in the presence of adequate d-tubo-curarine chloride, it is hydrolysed as rapidly as it is released, and an accumulation of acetylcholine sufficient to displace and replace the fixed d-tubo-curarine chloride is not possible. *It is clear that the intensity of motor nerve impulses reaching the neuromuscular junction of the skeletal muscles of the trunk is considerably reduced at the level of complete sensory loss.* Moreover, it may be assumed—and clinical experience with d-tubo-curarine chloride confirms this assumption—that the intensity of the motor impulses reaching this site progressively diminish as anæsthesia deepens and as the globus pallidus and, in turn, the red nucleus and other pontine and brain stem motor nuclei are successively depressed. When at length bulbospinal status has been achieved, the only efferent impulses which now reach the skeletal muscles of the body from a higher centre, at an effective intensity, *are the efferent impulses from the respiratory centre, which activate the crural fibres of the diaphragm*

The response of the subject during anæsthesia to the level of bulbospinal status differs materially from that of a bulbospinal animal preparation. In each instance, the vital medullary centres are functionally active, and although respiratory and cardiovascular reflexes are no longer subject to control from the strial, the hypothalamic, and the cortical level, they effectively mediate lung ventilation and all the reflexes essential to maintain blood pressure, cardiac output and efficient circulation Thus, vasopressor

and vasodilator reflexes, reflexes of the carotid sinus, and the various cardiac reflexes are effectively integrated at the medullary level. They differ strikingly in their response to proprioceptive stimulus. On the one hand, during anæsthesia at the bulbospinal level, *proprioceptive stimulus no longer produces reflex effects*, and with the exception of crural fibres of the diaphragm, skeletal muscles which do not exhibit lengthening and shortening reactions are absolutely toneless. On the other hand, the bulbospinal animal preparation *reacts in a characteristic fashion to proprioceptive stimulus*. Intersegmental reflexes and reflex spinal patterns are present, tendon reflexes are active, there is a vigorous plantar response, and skeletal muscles exhibit lengthening and shortening reactions. And even spinal man displays reflex activity, for segmental reflexes, flexor response, crossed extensor response and mass reflexes with facilitation can be elicited, and lengthening and shortening reactions are present in skeletal muscles.

When anæsthesia to the level of BULBOSPINAL STATUS has been achieved, except for impulses to the crural fibres of the diaphragm, motor impulses to skeletal muscles from a higher level are reduced to minimal proportions or they cease entirely, and the inability of the subject to react reflexly to proprioceptive stimulation at this level of anæsthesia may be attributed solely to a reversible interference with the integrity of the simple spinal reflex arc There is no evidence that proprioceptive receptors fail to initiate nerve impulses at this level of anæsthesia, and there is evidence that nerve fibres are functionally active and that their ability to conduct nerve impulses is unimpaired at this level of anæsthesia. Gros (1910) observed that nerve fibres were about six times more resistant to the action of volatile anæsthetics than the cells of the nervous system, and the fibres of the phrenic nerve conduct impulses efficiently during anæsthesia to the level of bulbospinal status. Forbes, McIntosh and Sefton (1916) observed action currents in the nerve of cats anæsthetised to the level of respiratory paralysis, and there is little doubt that the ability of the nerve fibres to conduct impulses is not depressed during anæsthesia to the level of bulbospinal status. When, however, di-ethyl ether vapour is applied to an isolated frog's nerve muscle preparation, it is observed when the nerve is stimulated that action currents can

parable size anæsthetised to the level of complete sensory loss. This result indicates that the quantum of acetylcholine released at the neuromuscular junction of the muscles of the trunk during the stage of complete sensory loss *is considerably smaller* than in a conscious or lightly anæsthetised subject, and this infers that *the intensity of the barrage of motor nerve impulses which reach the neuromuscular junction of these muscles during the stage of complete sensory loss is materially smaller than occurs in a conscious or lightly anæsthetised subject.* Moreover, if anæsthesia is maintained at the level of complete sensory loss, this original injection of 10 milligrams of d-tubo-curarine chloride will continue to produce full curarisation for three to five hours even in the presence of intense proprioceptive stimulation. This infers that the release of acetylcholine during the stage of complete sensory loss is so curtailed that in the presence of adequate d-tubo-curarine chloride, it is hydrolysed as rapidly as it is released, and an accumulation of acetylcholine sufficient to displace and replace the fixed d-tubo-curarine chloride is not possible. *It is clear that the intensity of motor nerve impulses reaching the neuromuscular junction of the skeletal muscles of the trunk is considerably reduced at the level of complete sensory loss.* Moreover, it may be assumed—and clinical experience with d-tubo-curarine chloride confirms this assumption—that the intensity of the motor impulses reaching this site progressively diminish as anæsthesia deepens and as the globus pallidus and, in turn, the red nucleus and other pontine and brain stem motor nuclei are successively depressed. When at length bulbospinal status has been achieved, the only efferent impulses which now reach the skeletal muscles of the body from a higher centre, at an effective intensity, *are the efferent impulses from the respiratory centre, which activate the crural fibres of the diaphragm*

The response of the subject during anæsthesia to the level of bulbospinal status differs materially from that of a bulbospinal animal preparation. In each instance, the vital medullary centres are functionally active, and although respiratory and cardiovascular reflexes are no longer subject to control from the strial, the hypothalamic, and the cortical level, they effectively mediate lung ventilation and all the reflexes essential to maintain blood pressure, cardiac output and efficient circulation. Thus, vasopressor

muscular junction of these muscles *progressively increases* as the quantum of acetylcholine at this site is *progressively diminished*; and, as anæsthesia deepens beyond the stage of complete sensory loss, the curare-like action of di-ethyl ether therefore becomes more intense, to a lesser degree because its concentration at the neuro-muscular junction is progressively increased, and to a very much greater degree because the quantum of acetylcholine released at this site is progressively diminished. When, at length, anæsthesia to the level of bulbospinal status has been achieved, *it can be supposed that the quantum of acetylcholine released at the neuromuscular junction of all skeletal muscles, except the crural fibres of the diaphragm, is so small that the concentration of di-ethyl ether at this site is effective in completely inhibiting neuromuscular transmission* At this level of anæsthetic depression, all skeletal muscles except the crural fibres of the diaphragm are toneless, and proprioceptive reflexes integrated at the bulbospinal or at the spinal level are, therefore, inactivated.

As anæsthesia deepens beyond the bulbospinal level, the respiratory centre is depressed and breathing ceases. Unless anæsthetic overdose is rapidly corrected, the combined effect of anoxia and anæsthetic overdose soon results in the depression of the vasomotor centre, and, as an end result, the cardiac centre fails.

This sequence of depression of the nuclear masses of the brain obtaining with di-ethyl ether serves as a pattern for a comparison of the behaviour of the other blood-borne anæsthetics in common clinical use.

Narcotics whose oil/water partition coefficient is less than unity, such as ethyl alcohol and acetone, depress the vital medullary centres soon after the cortical areas and the sympathetic entities of the hypothalamus have been depressed. Although insufficient is known of the physical properties and the sequence of uptake of local anæsthetics by the brain, the clinical signs which follow too great a concentration of a local anæsthetic in circulating blood suggest that they behave like ethyl alcohol and depress the vital medullary centres soon after the cortical areas and the sympathetic entities of the hypothalamus have been depressed. On this account, local anæsthetics and narcotics whose oil/water partition coefficient is less than unity, are unsuitable for use as blood-borne anæsthetics in clinical practice.

be measured in the nerve for some time after stimulation has failed to produce a muscle contraction. This effect may be explained by assuming that the transmission of the impulses is blocked at the neuromuscular junction as soon as an effective concentration of di-ethyl ether has been achieved at this site, and Ruttgers (1917) and Witanowski (1926) have shown that di-ethyl ether in an effective concentration produces a curare-like effect. These observers showed that a 0 25-1 per cent. of solution of di-ethyl ether abolished the effect of vagal stimulation in an isolated frog's heart-vagus preparation, and Witanowski showed that it was possible to inhibit the action of acetylcholine in this preparation without arresting the post-ganglionic release of acetylcholine at the neuromuscular junction. In the case of di-ethyl ether, this inhibition of the action of released acetylcholine was delayed until about ten minutes after exposure to the anæsthetic. This delayed effect can be attributed to the times taken to produce an effective concentration of di-ethyl ether at this site, and it cannot be attributed to excessive destruction of acetylcholine by cholinesterase, for it is known that this enzyme is destroyed or inhibited by blood-borne anæsthetics. Both Ruttgers and Witanowski failed to produce the effect with methyl and ethyl alcohol, and the fact that it cannot be produced with weak anæsthetics, and takes an appreciable time to achieve with potent anæsthetics, suggests that di-ethyl ether inhibits the action of acetylcholine when and if an effective concentration of this anæsthetic is achieved at the neuromusculor junction of skeletal muscle.

It is clear at the stage of complete sensory loss that the concentration of di-ethyl ether at the neuromuscular junction of the trunk muscles does not produce a curare-like effect; and it is unlikely that the concentration of di-ethyl ether at this site during anæsthesia to the level of bulbospinal status could inhibit neuromuscular transmission *if acetylcholine was released in normal amounts at the neuromuscular junction at this level of anæsthesia.* As anæsthesia deepens from the level of complete sensory loss, however, the intensity of motor impulses reaching the neuromuscular junction of all trunk muscles except the crural fibres of the diaphragm and, in turn, the quantum of acetylcholine released at this site, are progressively reduced With deepening anæsthesia it follows that the concentration of di-ethyl ether at the neuro-

not react to light indicate that depression of the vital medullary centres is imminent.

Thus, the blood-borne anæsthetics in common clinical use deviate in minor degrees from the pattern of behaviour of the adopted standard, di-ethyl ether, and precise knowledge of the reason for and the extent of such deviations would add greatly to the control of blood-borne anæsthetics in clinical practice. Apart from all else, this discussion of the probable sequence of depression of the nuclear masses of the brain with di-ethyl ether indicates that the *neurological signs manifest at the various levels of anæsthetic depression are release effects.* Although the signs of anæsthesia permit empiricists to control safely the uptake and maintenance of an effective concentration of an anæsthetic in the brain, it is thought that a picture of the gradual achievement of an effective concentration of the anæsthetic in successive nuclear masses of the brain, with the release effects that inevitably follow, makes for a clearer understanding, not only of what has actually happened but also of what can be expected to happen next.

References.

1. Bailey, Quote from Fulton, J. F (1938). *The Physiology of the Nervous System* p. 259. Oxford University Press, London
2. Barbour, H G. (1921). *Physiol. Rev.* **1**, 295.
3. Davison, C, & Selby, N. E. (1935). *Arch. Neurol. Phychiat. Chicago*, **33**, 570

3A Forbes, A., McIntosh, R, & Sefton, W. (1916) *Amer. J. Physiol.* **40**, 503.

4. Fulton, J. F. (1938). *The Physiology of the Nervous System* Oxford University Press, London.
5. Grinker, R (1937) *Neurology* 2nd Ed. p. 413. Thomas, Springfield.
6. Hess, W. R (1932) *Lancet*, ii, 1199.
7. Keller, A. D, & Hare, W. K. (1932) *Proc. Soc. exp Biol. N.Y.* **29**, 1069.
8. Kestenbaum, A. (1947) *Clinical Methods of Neuro-Ophthalmologic.* p. 259. W Heinemann, London.
9. King, L S, & Wislocki, G B. (1936). *Amer. J. Anat.* **58**, 421.
10. Riley, H A (1930) *Arch. Ophthal N.Y* **4**, 649, 885
11. Ruttgers, P (1917) *Zeit Biol* **76**, 1
12. Wislocki, G. B (1937) *Anat. Rec.* **69**, 361.
13. Witanowski, R W. (1926). *J. Physiol.* **62**, 88.

In general, anæsthetics with an oil/water partition coefficient greater than unity conform to, or can be made to conform to, the pattern of behaviour of di-ethyl ether. Minor deviations from this standard pattern that do occur can be attributed to variations, relative to di-ethyl ether, in the rate of uptake of the particular anæsthetic by particular areas of functional activity of the brain, for while the blood supply and narcotic susceptibility of each area of functional activity is a constant, its absorptive capacity varies as the oil/water partition coefficient of the paricular anæsthetic. Those anæsthetics whose oil/water partition coefficient is greater than unity and less than 14 resemble the pattern of behaviour of di-ethyl ether most closely; but the broad spacing between the depression of the several levels of functional activity, so characteristic of di-ethyl ether, is narrowed during anæsthesia with cyclopropane and chloroform, whose oil/water partition coefficients are very high. The oil/water partition coefficient of an anæsthetic is without doubt one of the factors determining the sequence of its absorption by particular cells of the central nervous system and, in turn, the sequence of depression of the several areas of functional activity of the brain. There are undoubtedly other relevant factors about which little is known. Thus, the hypothalamus is depressed earlier with morphia and the barbiturates than with di-ethyl ether. Wislocki (1937) showed that the hypothalamus is one of the most richly vascularized areas of the brain. King and Wislocki (1936) demonstrated that its vessels are more than ordinarily permeable to the passage of large molecules—and both morphia and the barbiturates have large molecules. Again, the corneal reflex appears to be abolished earlier during barbiturate and cyclopropane anæsthesia than when di-ethyl ether or chloroform is employed. This effect, however, may be more apparent than real, and may be due to the very rapid anæsthetic induction in standard sequence produced by the use of overpressure Or again, the gradual passive dilatation of the pupils during increasing depression of muscle tone with di-ethyl ether, chloroform and the barbiturates, is in contrast to the absence of passive dilatation of the pupils when a comparable degree of muscular relaxation is produced with cyclopropane. Moreover, with di-ethyl ether, extreme passive dilatation of the pupils can be safely achieved while with all other anæsthetics in common clinical use, widely dilated pupils that do

The transient action of ACh is due to its instability and to the presence of an enzyme, cholinesterase, which rapidly hydrolyses it to the almost inert choline and acetic acid. It is significant that cholinesterase is concentrated in the region of motor nerve endings where its presence is most required and this ensures that accumulation of ACh does not occur and that the muscle response is in keeping with the intensity of the nerve impulse.

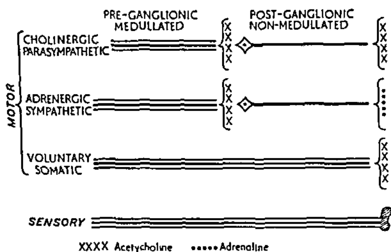


FIGURE 14.

Acetylcholine produces its biological response very rapidly. Brown and Eccles (1934) observed that the interval between preganglionic stimulation and the appearance of vagal inhibition in cats was about 0 15 seconds and when the post-ganglionic fibres of the vagus were stimulated, the delay was about 0·12 seconds.

All the pharmacological evidence agrees that the effective dose of ACh is very small, whether this data is observed on isolated tissue or on intact animals. Beznak (1934) found that only a few thousand molecules of ACh per cell was required to produce a measurable response on a frog's eserinised heart and Feldberg and Vartianan (1934) calculated that about 3 million molecules of ACh were released in the superior cervical ganglion per stimulus per cell. In experiments on isolated tissue Clark (1937) showed that a response can be elicited with a concentration of ACh of 1 in 10^9. He stated that the amount of ACh which must be fixed by a non-eserinised frog's heart to produce a 50 per cent. response

CHAPTER XXI

THE CHEMICAL TRANSMISSION OF *NERVE IMPULSES*

THE orderly depression of the motor nuclei of the brain has been seen to result in the progressive loss of muscle tone in skeletal muscles. The story of the mechanism of muscle excitation and inhibition is still incomplete, but the work of Loewi, Dale and many others has gone far to establish the presence of a chemical transmitter at the neuromuscular junction between motor nerve endings and the effector organ.

When sympathetic post-ganglionic fibres are stimulated, a substance is liberated at their peripheral nerve endings which is indistinguishable from adrenaline, for an injection of adrenaline affects all the structures innervated by these fibres in a manner identical with that following the stimulation of their motor nerves Hence, it can be assumed that adrenaline is the normal chemical transmitter of sympathetic post-ganglionic fibres, which Dale suggests should be termed "adrenergic fibres." Both the adrenaline secreted by the adrenal medulla and that liberated at the nerve endings of adrenergic nerves is rapidly destroyed by an enzyme, amine oxidase, which is normally present in blood and many tissues This enzyme prevents the accumulation of adrenaline and ensures that the response elicited in the effector organs of the sympathetic post-ganglionic fibres is in keeping with the intensity of the nerve impulses in these adrenergic nerves

There is much evidence that the post ganglionic fibres of the para-sympathetic, all the pre-ganglionic fibres of the autonomic system and the somatic motor nerves, liberate acetylcholine (ACh) at their peripheral nerve endings when they are stimulated. Brown, Dale and Feldberg (1936) conclusively demonstrated in normal mammalian muscle that ACh is capable of producing a muscle contraction which simulates that produced by the stimulation of its motor nerve, and there is the strongest probability that nerve impulses in these fibres, which Dale called "cholinergic fibres," are transmitted to the effector organ through the medium of *ACh*.

shown to possess about one-third of the ability of rats' brain to produce ACh. This precursor is, without doubt, identical with the complex found by other observers, for Corteggiani (1937) released ACh from brain cells by denaturation produced by 70°C for 3 minutes, Stedman and Stedman (1937) by denaturation produced by ether, and Loewi (1937) by denaturation produced by alcohol and acid alcohol.

Mann *et al* (1938) observed that the acetylcholine precursor is rapidly formed in the brain cells of rats *in vitro*. It is not destroyed by cholinesterase and eserine neither destroys the precursor nor appreciably inhibits its breakdown to free ACh. Both choline and ACh increase the rate of its synthesis by brain cells. Glucose, sodium lactate, and sodium pyruvate produce a much greater effect than choline upon the rate of its synthesis, while succinate has no effect and anoxia retards the synthesis of the precursor. These observers found that the amount of acetylcholine precursor rapidly achieved a maximal value in brain cells under optimal respiratory conditions obtained in the presence of oxygen and glucose, and they produced evidence to show that the limiting factor is neither choline nor a metabolic product of carbohydrate metabolism. They state, however: " It is at present doubtful whether glucose, lactate, or pyruvate give rise to a specific product combining with choline, or whether by a series of oxidative reactions they secure conditions suitable for the combination of choline to take place with another metabolite "—which, they suggest, consists of a specific protein. Figure 15 shows the scheme which they advance as a provisional mechanism of the synthesis of the acetylcholine precursor in tissue cells. This suggests that the limiting factor in this synthesis is a specific protein which behaves like an enzyme. When the cell becomes saturated with this specific protein, a limit is reached to the amount of acetylcholine precursor which can be formed, and, as shown in Figure 15, the precursor normally breaks down with the liberation of the specific protein and free ACh which is then hydrolysed to choline and acetic acid Hence, under optimal respiratory conditions, a choline cycle is established and the cell again becomes saturated with the specific protein and the acetylcholine precursor content of the cell again reaches its maximum value. The specific protein thus behaves as a catalyst and resembles an enzyme, for it brings

is 2 parts per million, and from these figures he estimated that the number of acetylcholine molecules required to produce a response on one heart cell would cover an area of only 0 3 square microns, or 1/6000 part of the total surface of the cell.

It is generally agreed that ACh acts as a mediator between the vagal nerve endings and heart cells, and the fact that it acts so rapidly in such low dilution and with the fixation of ACh sufficient to form a mono-molecular layer on only 1/6000 part of the cell surface, suggests that it produces its specific response on the heart by surface action. This conclusion is supported by Cook's work (1926) on the antagonism of ACh by methylene blue. His observations prove that methylene blue acts on the surface of a frog's heart, and he found that when the dye had penetrated into the interior of heart cells, it ceased to produce its antagonistic action on ACh. Since methylene blue acts as a specific antagonist to ACh, the simplest explanation of this fact is to suppose that both methylene blue and ACh act on the heart's surface.

All the cells upon which ACh acts contain a store of this substance, and a large store, for very prolonged stimulation is needed to produce signs of its exhaustion. Feldberg and Vartianan (1934) calculated that the acetylcholine store in the superior cervical ganglion was equivalent to the amount released by about 2,000 stimulations. Chang and Gaddam (1933) and a number of other observers agree that the ACh content of the heart is very much greater than the minimum effective heart dose. Beznak (1934) states that the frog's heart contains hundreds of times the quantity of ACh required to produce inhibition of the heart, but little if any of this ACh was present in a freely diffusible form and most of it was present in the cell interior in a combined form. Loewi (1935) agreed that ACh is present in the heart in some labile, non-diffusible combination which was neither active pharmacologically, nor was it liable to attack by cholinesterase.

The existence of an acetylcholine precursor has been demonstrated by Mann, Tannenbaum and Quastel (1938). They showed, when the eserinized cells of rats were denatured *in vitro* by chloroform, ether, or acid conditions, that the precursor is released from the cell interior and breaks down to ACh. It was not present in the kidney, the liver, the spleen or the testis, but rats' diaphragm was

denervated and a sufficient time elapses for the motor nerve endings in the muscle to degenerate, direct stimulation no longer produces an outflow of ACh. And it can be concluded that the breakdown of combined ACh and the release of free ACh is normally effected by an excitatory state produced in the peripheral motor nerve endings at the neuromuscular junction, produced by the passage of a nerve impulse in the motor nerve. Having been released thus, ACh is free to produce its characteristic action on the muscle, or to be hydrolysed by the enzyme, cholinesterase.

The specific nature of the biological action of ACh, the fact that it acts rapidly in such low concentrations and produces its action on about only $\frac{1}{6000}$ part of the cell surface, combine to suggest that ACh unites with specific receptors on the surface of muscle cells. This view receives support when the concentration-action curves of ACh are examined, for these curves, determined on a wide range of tissues, closely resemble the curve of the uptake of a chemical such as carbon monoxide by an active protein such as hæmoglobin. Clark (1937) stated that the only hypothesis based on known physio-chemical processes which provides an explanation for a considerable proportion of the facts reviewed, is the conception of specific receptors with which ACh forms a reversible combination Burn (1948) says: "We commonly suppose that muscle cells possess receptors and that a junction between a molecule of ACh and one of these receptors constitutes the stimulus to the muscle to contract." Thus the intensely specific action of ACh is presumed to depend upon the configuration of its molecule exactly fitting the configuration of these specific receptors on the surface of muscle cells, and having thus combined, it produces its characteristic depolarising action on skeletal muscle.

When curarine was injected, Dale, Feldberg and Vogt (1936) observed that the stimulation of a motor nerve released ACh but failed to produce a muscle contraction. This effect has been explained by supposing that released ACh must diffuse through a membrane before its molecules can reach its specific receptors and that the diffusion of ACh to these receptors was sufficiently retarded by the action of curarine on this membrane to permit cholinesterase to hydrolyse all the released ACh before it could reach and unite with these specific receptors. A simpler conception is to suppose that curarine fits the configuration of the ACh receptor on the cell

about the synthesis of the acetylcholine precursor and is itself regenerated. More recent work by Nachmansohin and Machado (1943) indicates that under strictly anærobic conditions an enzyme, choline acetylase, found to be present in all nerve fibres and muscles, affects the resynthesis of hydrolysed ACh at a rapid rate. The energy liberated by the breakdown of adenosino triphosphate is used for its resynthesis which is related to creatine phosphate and the main lines of intracellular enzyme organisation.

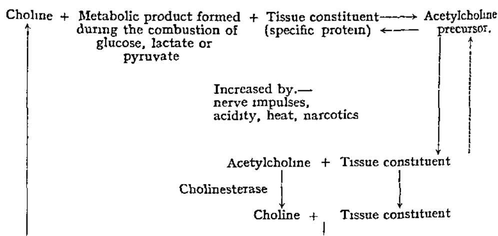


FIGURE 15 (MANN, TANNENBAUM & QUASTEL)

Combined ACh is pharmacologically inert and is not destroyed by cholinesterase; it is not diffusible or dialysable and is relatively stable at 37°C under optimum respiratory conditions obtained in the presence of oxygen and glucose. But it rapidly breaks down in a variety of conditions into free ACh which is then released at the synapse or neuromuscular junction. The normal mechanism for release is the arrival of an effective nerve impulse at the peripheral nerve endings of the synapse or neuromuscular junction, but Mann *et al* (1938) have shown *in vitro* that acid conditions or narcotics in a sufficient concentration inhibits the synthesis of combined ACh and at the same time, hasten its release and breakdown to free ACh

When a motor nerve is stimulated, or when an electrode is applied direct to the muscle surface, ACh is released at the neuromuscular junction of the muscle. If, however, the muscle is

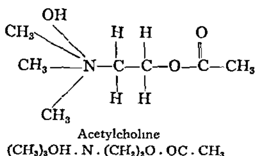
denervated and a sufficient time elapses for the motor nerve endings in the muscle to degenerate, direct stimulation no longer produces an outflow of ACh. And it can be concluded that the breakdown of combined ACh and the release of free ACh is normally effected by an excitatory state produced in the peripheral motor nerve endings at the neuromuscular junction, produced by the passage of a nerve impulse in the motor nerve. Having been released thus, ACh is free to produce its characteristic action on the muscle, or to be hydrolysed by the enzyme, cholinesterase.

The specific nature of the biological action of ACh, the fact that it acts rapidly in such low concentrations and produces its action on about only $\frac{1}{6000}$ part of the cell surface, combine to suggest that ACh unites with specific receptors on the surface of muscle cells. This view receives support when the concentration-action curves of ACh are examined, for these curves, determined on a wide range of tissues, closely resemble the curve of the uptake of a chemical such as carbon monoxide by an active protein such as hæmoglobin. Clark (1937) stated that the only hypothesis based on known physio-chemical processes which provides an explanation for a considerable proportion of the facts reviewed, is the conception of specific receptors with which ACh forms a reversible combination. Burn (1948) says: "We commonly suppose that muscle cells possess receptors and that a junction between a molecule of ACh and one of these receptors constitutes the stimulus to the muscle to contract." Thus the intensely specific action of ACh is presumed to depend upon the configuration of its molecule exactly fitting the configuration of these specific receptors on the surface of muscle cells, and having thus combined, it produces its characteristic depolarising action on skeletal muscle.

When curarine was injected, Dale, Feldberg and Vogt (1936) observed that the stimulation of a motor nerve released ACh but failed to produce a muscle contraction. This effect has been explained by supposing that released ACh must diffuse through a membrane before its molecules can reach its specific receptors and that the diffusion of ACh to these receptors was sufficiently retarded by the action of curarine on this membrane to permit cholinesterase to hydrolyse all the released ACh before it could reach and unite with these specific receptors. A simpler conception is to suppose that curarine fits the configuration of the ACh receptor on the cell

surface, and when, by substrate competition, curarine occupies these receptors, it prevents the fixation, and in turn inhibits the action of the normal substrate, ACh, which is then hydrolysed by cholinesterase. Cowan (1938) showed that the depolarising effect could be produced by the immersion of the satorious muscle in a solution of ACh, and that depolarisation of the muscle could be prevented by the previous application of curarine to the surface of the muscle. When Kuffler (1943) applied ACh discreetly to the end-plate region of his single nerve-muscle preparation, depolarisation of the muscle was produced, but when ACh was applied to the muscle surface other than the end-plate region, it neither depolarised the muscle nor produced a nerve impulse. And it can be concluded that specific ACh receptors are located in the end-plate region of the surface of muscle cells, and that curarine also fits the configuration of these receptors.

Acetylcholine is a strong base, whose formula is:



Acetylcholine
$(CH_3)_3OH \cdot N \cdot (CH_2)_2O \cdot OC \cdot CH_3$

It is probably fixed by skeletal muscles by the combination of its ammonium group with the carboxyl groups *(COOH) of* the cell protoplasm. Both ACh and curarine are quaternary ammonium compounds; when other quaternary ammonium compounds are examined, it is found that some produce an action on skeletal muscle similar to that of ACh *and others simulate the action of curarine.*

Ravenos (1937) investigated the combined action of ACh and various quaternary ammonium salts on isolated frog's heart and on the rectus abdominus and isolated gut of rats. He found that these quaternary ammonium salts antagonised or potentiated the action of ACh in the same manner in all three types of tissue. The result of his observations on the isolated frog's heart is seen in Table 47.

Ravenos found that the methyl series of quaternary ammonium salts $(CH_3)_3-N-R$, with relatively short side-chains depressed the action of the frog's myocardium in the same fashion as ACh. *This depressing action increased with the length of the side-chain,*

but soon reaches its greatest intensity and when the side-chain reached the octal group (C_8H_{17}), the salt produced no action on the frog's auricle. The salts of the ethyl series $(C_2H_5)_3-N-R$, like the salts of the methyl series with long side-chains, produce no action on the frog's auricle. The quaternary ammonium salts

TABLE 47.

ACTION OF THE QUATERNARY SALTS ON FROG'S AURICLE (Ravenos, 1936, 1937)

	Action of Salt.	Influence on the action of acetylcholine.
Series $(CH_3)_3-N-R$	Feebly depressing action.	Potentiation
Where R = CH_3 to C_4H_9	A depressing action which increases with the length of the side-chain R	Potentiation
Where R = C_8H_{17} . ..	No action	Powerful antagonism
Series. $(C_2H_5)_3-N-R$	No action	Antagonism
Where R = CH_3 to C_4H_9	No action	Antagonism

of the methyl series with short side-chains thus act as chemical transmitters of nerve impulses and it can be assumed that these salts are fixed by the same receptors as ACh and, having been thus fixed, they potentiate its action, for they possess the ability to transmit nerve impulses. Similarly, the salts of the methyl series with long side-chains, and those of the ethyl series, combine with acetylcholine receptors on the cell surface when present at the neuro-muscular junction in an effective concentration; but, since they lack the ability to transmit nerve impulses and because they have at the same time excluded the normal transmitter from these receptors, they antagonise the action of ACh. It is probable that it is the quaternary ammonium grouping in the molecular constitution of ACh, curarine, and the quaternary ammonium salts which

permits these compounds to combine with the same specific receptors in skeletal muscle, and that the individual side-chain of each compound determines its ability, on the one hand, to transmit nerve impulses and thus potentiate the action of ACh, or, on the other hand, determines its inability to act as a chemical transmitter of nerve impulses and so antagonise the action of the normal transmitter, ACh. Hence, there is reason to believe that ACh acts on the cell surface and that this action is produced by its fixation, through its quaternary grouping, to specific receptors located on the cell surface.

All the ACh released at the neuromuscular junction of the skeletal muscle, however, is not fixed by the specific receptors in muscle cells, and the number of acetylcholine molecules reaching and combining with the specific receptors on the surface of muscle cells is regulated by an enzyme, cholinesterase.

Cholinesterase is present in blood, in tissue fluids and in tissue cells, and is concentrated in the central nervous system and at the neuro-muscular junction of the skeletal muscle, where its presence is of most use. Mendel and Rudney (1943) have shown that two forms of cholinesterase are present in the body. They describe a very potent enzyme, true-cholinesterase, found in the brain, and a less potent pseudo-cholinesterase, found predominantly in plasma. The probable significance of these two forms of cholinesterase is considered later in this discussion. There is reason to believe that cholinesterase cannot destroy ACh in its combined form in the interior of tissue cells, but released ACh is very rapidly destroyed by cholinesterase, which hydrolyses it to the almost inert choline and acetic acid. Many molecules of released ACh are destroyed by cholinesterase at the neuromuscular junction before they can reach and combine with their specific receptors on the cell surface. Those molecules which escape hydrolysis, attain fixation with their specific receptors and act as chemical transmitters of the nerve impulse. But the continued rapid hydrolysis of ACh at length effects the disengagement and subequent destruction of these fixed acetylcholine molecules after they have served their purpose as chemical transmitters and this ensures that the specific receptors shall be free to accept ACh released by the next nerve impulse in the motor nerve In normal conditions of life, the amount of ACh released, and the amount of released ACh escaping destruction by

cholinesterase and subsequently fixed by muscle receptors, are such that the muscle response is in keeping with the intensity of the nerve impulse in the motor nerve.

The evidence discussed suggests that, in consequence of the excitation of peripheral motor nerve endings produced by a motor

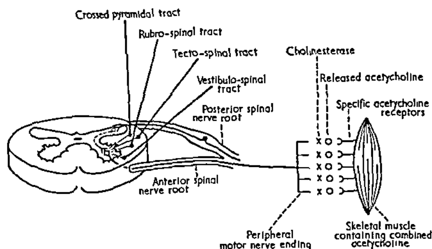


FIGURE 16.

nerve impulse of effective intensity, ACh is released from the cell interior to the cell surface at the neuromuscular junction in amounts which correspond with the intensity of the nerve impulse. This is followed by the combination of released ACh with specific acetylcholine receptors on the cell surface; the number of receptors occupied varies as the amount of ACh released. Once fixed, ACh produces a muscle contraction which corresponds in magnitude with the intensity of the motor nerve impulse. Rosenblueth's view (1935) of the chain of events following the stimulation of a motor nerve coincides with these conclusions and may be summarised thus: An excitatory state at the neuromuscular junction ——→ conducted disturbance in the effector ——→ liberation of the transmitter ——→ combination of the transmitter with the receptive substance ——→ specific reaction of the effector.

Figure 16 is a diagrammatic representation of the entities concerned in the chain of events which results in the contraction of skeletal muscle, and it is clear that the ability of normal skeletal

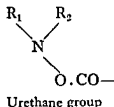
muscle to contract may be abolished in a freely reversible manner in the following ways:—

1. Acetylcholine released at the neuromuscular junction in normal amounts *may be destroyed* before it can reach and combine with specific acetylcholine receptors on the surface of skeletal muscle cells.
2. Acetylcholine released at the neuromuscular junction in normal amounts *may be unable to attain fixation* with specific acetylcholine receptors on the surface of skeletal muscle cells.
3. Acetylcholine *may not be released in normal amounts* at the neuromuscular junction of skeletal muscle cells.

1. Released ACh is rapidly destroyed by the enzyme cholinesterase and the fixation of ACh by cholinesterase results in its hydrolysis into choline and acetic acid. There is no evidence that the conditions which obtain during clinical anæsthesia result in an increase in the amount or the potency of cholinesterase present at the neuromuscular junction of skeletal muscles. On the contrary, narcotics in a sufficient concentration inhibit the action of cholinesterase. This result is produced rapidly in the case of chloroform and urethane and it occurs more slowly with the barbiturates. Crude or semi-crude extracts of curarine also inhibit the action of cholinesterase. Harris and Harris (1941) report that intocostrin, which is a semi-crude curarine preparation, inhibits the action of cholinesterase. McIntyre and King (1943) state that pure d-tubocurarine chloride has no measurable effect upon this enzyme and Harris and Harris (1944) found that pure d-tubo-curarine chloride did not inhibit cholinesterase at low concentrations, but had a slight inhibitory effect at higher concentrations. Hence, the evidence indicates *that the hydrolysis of ACh is not accelerated, but may be actually retarded in the conditions obtaining in clinical anæsthetic practice.*

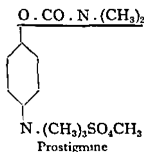
There is a group of substances called anticholinesterases which are administered with the express purpose of inhibiting the action of cholinesterase, and in this fashion hastening the accumulation of released ACh. Stedman and Stedman (1931) suggest that anticholinesterases have side-chains which permit them to unite with

the same combining group of cholinesterase as does ACh. They differ, however, from ACh, for the fixation of ACh with cholinesterase results in its rapid hydrolysis, but cholinesterase does not possess the ability to dissociate or destroy anticholinesterase fixed in this manner. The combining group of anticholinesterases is the urethane group in which R_1 and R_2, or both, are alkyl or phenol groups. If this urethane grouping is replaced by an hydroxyl group (OH), the anticholinesterase activity of the substance is destroyed.



Urethane group

Anticholinesterases inhibit the action of cholinesterase in blood, in skeletal and smooth muscle, in the myocardium, and in the brain. In clinical medicine the two best known anticholinesterases are eserine and prostigmine. Eserine, which is a tertiary ammonium compound, acts on the central nervous system as a potent stimulant. In larger doses it produces powerful generalised convulsions, presumably by inhibiting the potent true cholinesterase which is present in the brain, and thus permitting the rapid accumulation of excess of ACh at central synapses. It is therefore not suitable for use in clinical anæsthetic practice; nor can a useful inhibiting effect on the cholinesterase of skeletal muscle be obtained without at the same time producing its stimulating action on the para-sympathetic system. The related substance, prostigmine, which is a quaternary ammonium compound, has a greater selective action than eserine on the cholinesterase of skeletal muscle, the pseudo-cholinesterase of Mendel and Rudney. It also acts less markedly upon the viscera and the para-sympathetic system, but in large doses it has a depressing action on the central nervous system. The structural formula of prostigmine is shown below with its urethane group underlined. It competes with ACh, for the ACh receptors on the enzyme cholinesterase, and when the concentration of prostigmine reaches a certain critical concentration, by an adsorption displacement mechanism, it occupies these receptors to the exclusion of the normal biological substrate, ACh, and so inhibits



Prostigmine

the action of the enzyme. In clinical anæsthetic practice, prostigmine is employed to hasten recovery from curarisation. In doses one-tenth of the amount of d-tubo-curarine chloride used; it is injected intravenously *after* the injection of appropriate atropine, and *after* sufficient time has elapsed for this atropine to paralyse parasympathetic effectors. No anxiety has been experienced on more than 2000 occasions after curarised electrical shock therapy, when 2½ mgs. of prostigmine was injected intravenously, 5 to 7 minutes after the intravenous injection of atropine gr. 1/50. But it has been noted, when the subject is under-atropinized, and/or if prostigmine is injected with, or too soon after, the atropine, that parasympathetic effects of varying intensity may occur. Two deaths from cardiac failure have recently been reported a very short time after the intravenous injection of prostigmine (2½ mgs. McIntosh, 1949 and 2 mgs Clutton-Brock, 1949), and in each instance a small dose of atropine gr. 1/100th was administered *at the same time* as the prostigmine.

2. The fixation of ACh released in normal amounts at the neuro-muscular junction of skeletal muscles can be entirely prevented by the continued presence of an effective concentration of d-tubo-curarine chloride at this site and this results in complete loss of muscle tone in skeletal muscles When 30 mgs. of d-tubo-curarine chloride are injected intravenously into a conscious healthy subject weighing about 70 kilos, ACh is released at the neuro-muscular junction in normal amounts, but complete loss of muscle tone is produced in all skeletal muscles and, if the subject is adequately oxygenated, these muscles will regain their tone in about 30 minutes. This phenomenon is an *adsorption displacement mechanism*: evidence has been discussed which indicates that d-tubo-curarine chloride present at the neuromuscular junction at a certain critical concentration successfully competes with released ACh for the ACh receptors on the surface of muscle cells. Its fixation by these receptors not only excludes the normal biological substrate ACh but also produces complete loss of muscle tone in skeletal muscles, for d-tubo-curarine chloride does not possess the ability to transmit nerve impulses. Since the phenomenon is an adsorption displacement mechanism, and because d-tubo-curarine is an inert non-reactive substance, its effect upon muscle tone is freely reversible. As soon as the accumulating ACh reaches a

certain critical concentration at the neuromuscular junction of skeletal muscles—and this accumulation will occur fairly rapidly in a conscious subject who reacts to external stimulus and releases ACh in normal amounts—d-tubo-curarine chloride is displaced from these muscle receptors and its place is taken by ACh; with the fixation of the normal transmitter, muscle tone is again restored in skeletal muscle.

When a local anæsthetic in an effective concentration is injected into a skeletal muscle, it inhibits not only the initiation of proprioceptive impulses in the muscle itself, but also neuromuscular transmission in the same manner as d-tubo-curarine chloride. The evidence of Ruttgers and Witanowski indicates that blood-borne anæsthetics above a certain concentration inhibit the action of ACh in a manner similar to that of d-tubo-curarine chloride. But it is only during blood-borne anæsthesia deeper than complete sensory loss that the deficient release of ACh reduces its concentration at the neuromuscular junction to such a small quantum that the concentration of blood-borne anæsthetic present at this site becomes effective as an inhibitor of neuromuscular transmission. Hence substances *which fit the configuration of the ACh receptors of skeletal muscle, but which do not possess the ability to transmit nerve impulses* prevent the fixation and inhibit the action of ACh, when they are present in an effective concentration at the neuromuscular junction in skeletal muscle. Such an effective concentration can be readily achieved safely with local anæsthetics and with d-tubo-curarine chloride; they are effective inhibitors of neuromuscular transmission in conscious subjects in whom ACh is released in normal amounts at the neuromuscular junction of skeletal muscles.

3. Finally, muscle tone may be abolished by inhibiting the release of ACh in normal quanta at the neuromuscular junction of skeletal muscles· and *this is the dominant, but not the only, mechanism of the production of loss of muscle tone in skeletal muscles during local and blood-borne anæsthesia.*

When a local anæsthetic in an effective concentration is injected with anatomical accuracy into the vicinity of a peripheral nerve, the excitability and conductivity of the nerve is abolished in a reversible manner at the zone of the local anæsthetic nerve block, and in clinical practice, local anæsthetics are used for the reversible

abolition of impulse conduction in sensory and motor peripheral nerves. Because of the anæsthetic block of *the lower motor neurone*, motor impulses fail to reach the peripheral nerve endings of the motor nerve and, in the absence of an excitatory state at the neuromuscular junction served by the block motor nerve, ACh is not released at this site. Hence, when all the motor nerves to a skeletal muscle are blocked by local anæsthetic, the muscle becomes toneless and will remain so until impulse conduction and, in turn, the normal release of ACh are restored. During spinal anæsthesia, an effective concentration of a local anæsthetic is brought into contact with spinal nerve roots as they cross the spinal subarachnoid space, and the excitability and conductivity of these nerve roots is abolished in a reversible manner. Since the anterior spinal nerve root is the final common pathway of all motor impulses leaving a given spinal segment, it follows during spinal anæsthesia that all motor impulses, irrespective of their origin, fail to reach the neuromuscular junction of the skeletal muscles innervated through this spinal segment, and ACh is not released at the neuromuscular junction of these muscles, which become toneless and remain so until impulse conduction in the anterior spinal nerve root is restored.

Blood-borne anæsthetics do not depress the excitability or the conductivity of nerve fibres in the concentrations used in clinical anæsthetic practice, but evidence has been discussed which indicate that impulse formation in *upper motor neurones* is gradually reduced as the anæsthetic depression of the brain proceeds level by level There is also evidence that when at length anæsthesia to the level of bulbo-spinal status has been achieved, the integration of motor impulses at the supramedullary level has to all intents and purposes ceased, and efferent impulses which reach the anterior horn cells of the spinal cord in the descending tracts — namely, the crossed pyramidal, the vestibulo-spinal, the rubrospinal, and perhaps the reticulo-spinal tracts—are reduced to minimal proportions or have entirely ceased. In this instance the only nerve impulses which may reach the anterior horn cells of a given spinal segment are those initiated in the proprioceptive receptors of the muscles of this or adjacent segments, and they are integrated in the cells of the posterior nerve ganglion and the connector neurone of the spinal segment. There

is no evidence that either the proprioceptive receptor, the afferent neurone and the connector neurone of the spinal reflex arc or its efferent neurone, the final common pathway of efferent impulses, are inactivated during blood-borne anæsthesia. This suggests that when bulbo-spinal status has been achieved during blood-borne anæsthesia, nerve impulses reaching the anterior horn cells and, in turn, the peripheral motor nerve endings of a spinal segment, are reduced to small proportions, but have not entirely ceased, and also that the release of ACh at the neuromuscular junction of skeletal muscles is small but has not ceased. But at this level of blood-borne anæsthesia, loss of muscle tone is absolute in all skeletal muscles except the crural fibres of the diaphragm. This complete loss of muscle tone is attributed in *a major degree* to the absence of efferent impulses integrated at a supramedullary level; the inhibition of the small quantum of ACh released by intersegmental reflexes integrated, at a medullary or spinal level, can be attributed to the concentration of the blood-borne anæsthetic at the neuromuscular junction of skeletal muscles which is attained at this level of anæsthesia. The escape of the crural fibres of the diaphragm can also be fitted into the picture. Since the respiratory centre is functionally active at this level of anæsthesia, the normal barrage of nerve impulses from the centre reaches the neuromuscular junction of the crural fibres of the diaphragm and in turn affects the release of the normal quantum of ACh. The concentration of blood-borne anæsthetic at this site is consequently insufficient to inhibit this normal quantum of ACh by adsorption displacement, and the crural fibres of the diaphragm retain their tone and respond normally to impulses integrated by the respiratory centre

It can be concluded when the motor nerves to skeletal muscles are blocked with local anæsthetic, that *a reversible lower motor neurone* lesion is produced; and, because efferent impulses fail to reach the peripheral motor nerve endings in the muscle, ACh is not released at its neuromuscular junction and the muscle becomes toneless. During blood-borne anæsthesia of sufficient depth, the reversible anæsthesia depression of *upper motor neurones* significantly reduces the release of ACh at the neuromuscular junction of all skeletal muscles, except the crural fibres of the diaphragm to the minimum, and the concentration of the blood-borne anæsthetic at

abolition of impulse conduction in sensory and motor peripheral nerves. Because of the anæsthetic block of *the lower motor neurone*, motor impulses fail to reach the peripheral nerve endings of the motor nerve and, in the absence of an excitatory state at the neuromuscular junction served by the block motor nerve, ACh is not released at this site. Hence, when all the motor nerves to a skeletal muscle are blocked by local anæsthetic, the muscle becomes toneless and will remain so until impulse conduction and, in turn, the normal release of ACh are restored. During spinal anæsthesia, an effective concentration of a local anæsthetic is brought into contact with spinal nerve roots as they cross the spinal subarachnoid space, and the excitability and conductivity of these nerve roots is abolished in a reversible manner. Since the anterior spinal nerve root is the final common pathway of all motor impulses leaving a given spinal segment, it follows during spinal anæsthesia that all motor impulses, irrespective of their origin, fail to reach the neuromuscular junction of the skeletal muscles innervated through this spinal segment, and ACh is not released at the neuromuscular junction of these muscles, which become toneless and remain so until impulse conduction in the anterior spinal nerve root is restored.

Blood-borne anæsthetics do not depress the excitability or the conductivity of nerve fibres in the concentrations used in clinical anæsthetic practice, but evidence has been discussed which indicate that impulse formation in *upper motor neurones* is gradually reduced as the anæsthetic depression of the brain proceeds level by level. There is also evidence that when at length anæsthesia to the level of bulbo-spinal status has been achieved, the integration of motor impulses at the supramedullary level has to all intents and purposes ceased, and efferent impulses which reach the anterior horn cells of the spinal cord in the descending tracts — namely, the crossed pyramidal, the vestibulo-spinal, the rubrospinal, and perhaps the reticulo-spinal tracts—are reduced to minimal proportions or have entirely ceased In this instance the only nerve impulses which may reach the anterior horn cells of a given spinal segment are those initiated in the proprioceptive receptors of the muscles of this or adjacent segments, and they are integrated in the cells of the posterior nerve ganglion and the connector neurone of the spinal segment. There

CHAPTER XXII

THE USE OF D-TUBO-CURARINE CHLORIDE IN CLINICAL ANÆSTHETIC PRACTICE

THE arrow poison of the South American Indians is called curare. It is a watery extract of the stems, bark and leaves of a number of poisonous plants which are native to the thousands of square miles of country that comprises and surrounds the basins of the Orinoco and Amazon rivers, and their tributaries. Many species of plant from this area yield curare, but botanists are uncertain of the particular plant or plants from which the best yield of curare is obtained. The most potent of the curare alkaloids appear to be derived from Strychnos toxifera and Chondodendrom tomentosum. Although the preparation of arrow poison has almost ceased, the crude botanical material which yields curare is collected in South America and has become a commercial product, exported to Europe and North America for extraction and purification. So little is known of the botanical origin of curare, that the crude material is assayed for its curare content before it leaves South America.

Curare has long been known, and was first mentioned in 1595 by Sir Walter Raleigh. It was introduced to medicine about 1828; in the later part of the last century, and stimulated by the work of Claude Bernard, curare was used in France for the treatment of tetanus, chorea and other similar conditions. The results obtained were almost uniformly bad, for it had not been realised that the crude material imported from South America contained two active principles which differ in their pharmocological action. The variations in the botanical composition of the imported material, the hygroscopic nature of the crude extract, and its tendency to turn into a brownish, yellow, syrupy, resinoid mass on exposure to air hindered the isolation of these two active principles of curare for many years Long before they were identified, it was realised that some samples of the crude material produced paralysis

this site is sufficient to inhibit completely the action of the small quantum of ACh released, and these muscles become toneless. Finally, d-tubo-curarine chloride may be employed in clinical anæsthetic practice to produce complete loss of tone in skeletal muscles, for in effective doses it inhibits the neuromuscular transmission of nerve impulses to skeletal muscles. Since d-tubo-curarine chloride is a recent acquisition to clinical anæsthetic practice, it is proposed to discuss this anæsthetic adjuvant in detail.

References.

1. Beznak, A B. L (1934) *J. Physiol* **82**, 129
2. Brown, G. L., Dale, H. H., and Feldberg, W. (1936) *J. Physiol.* **87**, 394
3. Brown, G L., and Eccles, J C (1934) *J. Physiol.* **82**, 211, 242.
4. Burn, J. H. (1948). "The Background of Therapeutics," p 235 Oxford University Press, London.
5. Chang, H. C, and Gaddam, J. H (1933). *J. Physiol.* **79**, 225.
6. Clark, A J. (1937). *Handbuch der experimentellen Pharmakologie Vierter Band.* p 21, 90. Julius Springer, Berlin.
7. Clutton-Brock, J. (1949) *Brit Med J.* **1**, 1007.
8. Cook, R. P. (1926). *J. Physiol.* **62**, 160.
9. Corteggiana, E (1937) *C R. Soc Biol* Paris. **125**, 949
10. Cowan, S L. (1938) *J. Physiol.* **88**, 3P.
11. Dale, H H, Feldberg, W., and Vogt, M. (1936). *J. Physiol* **86**, 353. (1936-37) *J. Physiol.* **88**5P
12. Feldberg, W, and Vartianan, A (1934). *J. Physiol* **83**, 103.
13. Harris, M M, and Harris, R S. (1941) *Proc. Soc. exp Biol. N Y.* **46**, 619, 623. Ibid. (1944) **56**, 223
14. Kuffler, S. W. (1943) *J. Neurophysiol.* **6**, 99
15. Loewi, O (1937). *Naturwissenschaften*, **25**, 416. (1935). *Proc. roy. Soc* **118**, 299
16. Macintosh, R R (1949) *Brit. Med J.* **1**, 852.
17. Mann, P J G, Tennenbaum, M., and Quastel, J H. (1938) *Bio chem. J* **32**, 243.
18. Mendel, B, and Rudney, H (1943). *Bio. chem J.* **37**, 59
19. McIntyre, A. R, and King, R E. (1943) *Science.* **97**, 68.
20. Nachmansohn, D, and Machado, A L (1943) *J. Neurophysiol.* **6**, 397.
21. Ravenos, J (1937) *Quart J. exp Physiol.* 26. (1936-37) *J. Physiol* **83**, 5D.
22. Rosenblueth, A (1935) *Quart Rev Biol* **10**, 334
23. Stedman, E, and Stedman, E (1926) *Bio chem J.* **62**, 88 (1931) *Bio. chem. J* **25**, 1147. (1937). *Bio. chem. J.* **31**, 817

CHAPTER XXII

THE USE OF D-TUBO-CURARINE CHLORIDE IN CLINICAL ANÆSTHETIC PRACTICE

THE arrow poison of the South American Indians is called curare. It is a watery extract of the stems, bark and leaves of a number of poisonous plants which are native to the thousands of square miles of country that comprises and surrounds the basins of the Orinoco and Amazon rivers, and their tributaries. Many species of plant from this area yield curare, but botanists are uncertain of the particular plant or plants from which the best yield of curare is obtained. The most potent of the curare alkaloids appear to be derived from Strychnos toxifera and Chondodendrom tomentosum. Although the preparation of arrow poison has almost ceased, the crude botanical material which yields curare is collected in South America and has become a commercial product, exported to Europe and North America for extraction and purification. So little is known of the botanical origin of curare, that the crude material is assayed for its curare content before it leaves South America.

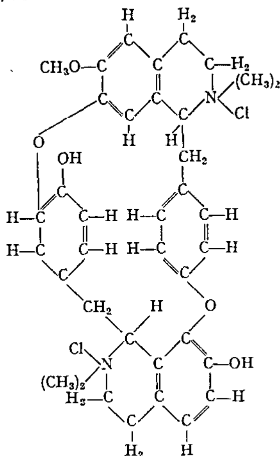
Curare has long been known, and was first mentioned in 1595 by Sir Walter Raleigh. It was introduced to medicine about 1828; in the later part of the last century, and stimulated by the work of Claude Bernard, curare was used in France for the treatment of tetanus, chorea and other similar conditions. The results obtained were almost uniformly bad, for it had not been realised that the crude material imported from South America contained two active principles which differ in their pharmocological action. The variations in the botanical composition of the imported material, the hygroscopic nature of the crude extract, and its tendency to turn into a brownish, yellow, syrupy, resinoid mass on exposure to air hindered the isolation of these two active principles of curare for many years. Long before they were identified, it was realised that some samples of the crude material produced paralysis

of skeletal muscles, while other samples were cardiac depressants and produced a convulsive action closely resembling that of strychnine. At length Boehm (1886-1897) found that the pharmacological properties of crude curare extracts were fairly characteristic of the containers in which they were packed for export and he divided curare into three types; calabash curare, pot curare, and tube curare. In each type of curare he found two active principles in varying proportions. The first active principle proved to be a *quaternary alkaloid base which Boehm termed "curarine"* and it fulfilled the classical test on frogs originated by Claude Bernard. This test is a "sine qua non" of curarine; its object is to demonstrate paralysis of muscle by a mechanism which acts distal to the motor nerve. Boehm obtained calabash curarine from calabash curare, proto-curarine from pot curare, and tubo-curarine from tube curare, and these curarines behaved like quaternary ammonium bases and consisted of hydrated quinolines. The second alkaloidal fraction isolated by Boehm from the crude curare extract consisted of *tertiary alkaloids which he termed "curines"* Curines possess little or no paralysing action on nerve-muscle preparations. They are convulsants and cardiac depressants, and it was the presence of curines in the curare extracts used by the early French observers that were responsible for the unsatisfactory results obtained by them. Boehm showed that all curares are either neutral or slightly acid in aqueous solution and on standing, clear aqueous solutions of crude or semi-crude curarine, including Intocostrin which contains a mixture of alkaloids, lose their potency and become brownish yellow and turbid with the formation of a precipitate; McIntyre (1947) however, qualifies this statement by reporting that he has used a sample of Intocostrin in this condition eighteen months after its preparation, and it had retained 97 per cent. of its original potency.

It was not until 1935 that King isolated *d-tubo-curarine*, which was the first quaternary curare alkaloid to be obtained in pure crystalline form He successfully separated curarines from curines in an extract of tube curare provided by the museum of the Pharmaceutical Society, and purified the quaternary base to obtain pure tubo-curarine. The pure tubo-curarine precipitated in micro-crystals with a characteristic sheen, and the anhydrous salt proved

[1] Intocostrin contains about 60% of d-tubo-curarine and 40% of other quaternary and tertiary bases of curare.

to be dextro-rotatory. D-tubo-curarine chloride has the formula $C_{37}H_{43}O_5N_2Cl_2$; its structural formula is shown below.



d-Tubo-curarine chloride.

When used clinically in aqueous solution, d-tubo-curarine chloride is not an irritant. It produces neither tissue damage when injected subcutaneously or intramuscularly, nor hæmolysis or thrombosis when injected intravenously. The writer has injected 30 mgs. of an aqueous solution of d-tubo-curarine chloride every second day into the same vein of a particular subject during a course of eighteen consecutive injections, without producing a thrombosis in this vein. When an aqueous solution of d-tubo-curarine chloride is mixed with the standard solution of pentothal, a white precipitate forms. This precipitate is an irritant, for when injected intravenously—and sometimes even when intravenous pentothal is immediately followed by an aqueous solution of d-tubo-curarine chloride, injected intravenously through the same

needle—the vein may thrombose; the incidence of thrombosis from this cause varies considerably, however, from subject to subject. *Alternatively, d-tubo-curarine chloride is supplied in an aqueous* solution with glycerine and alcohol, and this solution is compatible with pentothal. At first the concentrations of glycerine and alcohol employed were too strong and the solution, either alone or combined with pentothal, produced frequent thrombosis. The concentration of glycerine and alcohol have now been reduced, and the incidence of thrombosis which follows the intravenous *injection of this solution is of about the same order* as when intravenous pentothal is immediately followed by d-tubo-curarine chloride in aqueous solution.

The absorption of d-tubo-curarine chloride is very sluggish, if, indeed, it is absorbed at all, into circulating blood through unbroken skin. Absorption from mucous surfaces is rather slow, but it is relatively rapid from serous surfaces. It may be adminis*tered orally, subcutaneously, intramuscularly, or intravenously*, but in clinical practice the intravenous method of approach to circulating blood is the one most commonly employed.

About three minutes after the intravenous injection of d-tubo-curarine chloride, skeletal muscles become toneless. Loss of muscle tone occurs first in small muscle groups, viz. the extrinsic muscles of the eye, the muscles of the eyelids, the facial muscles, and those of the ears, the fingers and the toes, the muscles of the head and neck, and those of the throat and glottis; then in large muscle groups, viz the muscles of the extremities, next in the muscles of the trunk, and finally in the intercostal muscles and the sternocostal fibres of the diaphragm. This sequence of loss of muscle tone in skeletal muscles during curarisation is seen to be identical with the order in which striated muscles are involved in myasthenia gravis, and the probable significance of this will be discussed later.

[illegible]e needs of clinical anæsthetic practice are completely satisfied [illegible] degree of curarisation which produces loss of muscle tone in an ex[illegible]ercostal muscles and the sternocostal fibres of the [illegible] Should that concentration of d-tubo-curarine chloride [illegible] blood be slightly increased—and this can readily [illegible] with [illegible]al anæsthetic practice—the crural fibres of the [illegible] their tone, *respiratory movements cease*, and the

volume of lung ventilation falls to zero. Except when d-tubo-curarine chloride is inadvertently administered to a myasthenic subject, this is the greatest degree of curarisation likely to be encountered in clinical practice: in the absence of anoxia, autonomic activity is not affected, and smooth muscle responds to appropriate stimulus. For example, it is not uncommon to see a wave of peristalsis pass down the ureters at this degree of curarisation.

If, however, the concentration of d-tubo-curarine chloride in circulating blood was materially increased above that required to paralyse the crural fibres of the diaphragm—*and this is likely to occur in clinical anæsthetic practice only by accident or through ignorance, as when d-tubo-curarine chloride is administered to a myasthenic subject*—both the sympathetic and the para-sympathetic ganglia are paralysed in a manner that is analogous to the effect produced by nicotine, and nerve impulses in preganglionic fibres are blocked at the sympathetic and para-sympathetic ganglia. Sollman (1926) says that the susceptibility of the autonomic system to curarisation is as follows: Cardio-inhibitory; then chorda secretory, sweat, pilomotor, dilator and constrictor of the pupil; then the bulbar and sacral vasodilators; next cutaneous vasodilator, and finally the abdominal vasoconstrictors. At this degree of curarisation, the motor apparatus of the heart is unaffected and a very much larger blood concentration of d-tubo-curarine chloride would be required to produce loss of muscle tone in the myocardium. Cole (1946) states that the non-anoxic lethal heart dose of curarine is a thousand times the dose required to produce loss of muscle tone in skeletal muscles.

Thus, as the blood concentration of d-tubo-curarine chloride is gradually increased, the picture in Man is one of the progressive inhibition of the biological activity of acetylcholine, first at the neuromuscular junction of skeletal muscle; *then*, after a material increase in its blood concentration, at the sympathetic and para-sympathetic ganglia; *finally*, when a massive blood concentration of d-tubo-curarine chloride is achieved, in the heart itself. Hence, in a subject in whom the synthesis and release of combined acetylcholine is normal—and this includes all subjects except those suffering from myasthenia gravis—*d-tubo-curarine chloride in the dosage employed in clinical anæsthetic practice does no more than inhibit*

the transmission of nerve impulses at the neuromuscular junction of all skeletal muscles. When inadvertent overdose occurs with this clinical dosage no additional effect, other than the reversible paralysis of the crural fibres of the diaphragm, is likely. If subjects with myasthenia gravis are excluded, it follows, when clinical dosage is employed, that the sole action of d-tubo-curarine chloride in Man is the reversible loss of muscle tone in skeletal muscles. This conclusion is, on examination, found to be valid, for the upset of physiological regulation and metabolic activity of an adequately oxygenated subject during clinical curarisation *can be attributed solely* to the results which follow the complete loss of muscle tone in skeletal muscles.

When curarisation has progressed to the stage of paralysis of the intercostal muscles and the sternocostal fibres of the diaphragm, a tracheal tug is present, and breathing is shallow. The tracheal tug is produced on inspiration by the contraction of the un-inhibited crural fibres of the diaphragm. On inspiration, the downward pull of these fibres on the central tendon of the diaphragm is transmitted to the pericardium, and through it to the root of the lungs and in turn to the trachea and the thyroid cartilage. A tracheal tug is pathognomonic of this degree of curarisation and its intensity varies as the depth of breathing. The downward movement of the thyroid cartilage (the Adam's apple) on inspiration is marked when breathing is relatively deep, as in curarisation during nitrous oxide, oxygen and ether anæsthesia; it may be slight and inconspicuous, but nevertheless elicited on palpation, when curarisation is combined with the shallow breathing produced during cyclopropane or deep barbiturate anæsthesia. When a tracheal tug is present, this degree of curarisation has produced a diminution of the metabolic rate of the subject; but, in spite of his reduced oxygen demands, the volume of lung ventilation may be insufficient adequately to oxygenate a subject breathing air at mean sea level or an anæsthetic atmosphere of comparable oxygen content. In this instance, the oxygen tension of the atmosphere breathed must be increased and/or the mass movement of sufficient oxygen to alveolar air must be provided by the manual rhythmic compression of the reservoir of the anæsthetic apparatus.[1]

[1] During curarisation the only efficient method of artificial respiration is based on the forcible insufflation of oxygen into alveolar air. Methods of artificial respiration which depend upon rhythmic external pressure on the thoracic cage are useless

In the absence of other factors, the tracheal tug disappears during recovery from deep blood-borne anæsthesia and/or from curarisation *as soon as the intercostal muscles and the sternocostal fibres of the diaphragm regain their tone.* The tracheal tug is also abolished of necessity when breathing ceases, and respiratory arrest during blood-borne anæsthesia and curarisation may be produced in a number of ways.

Absolute oxygen lack produces depression of the respiratory centre with respiratory arrest in 3 - 8 minutes in a normal subject, and this result occurs even more rapidly in an anæsthetised curarised subject. Exposure to an anæsthetic atmosphere containing oxygen at an adequate partial pressure, respiratory obstruction and/or glottic spasm produced by irritants, may result in anoxia during anæsthetic induction. When, however, respiratory obstruction is avoided and the oxygen content of the anæsthetic atmosphere is adequate, respiratory arrest may still occur. In animals, an excessive rise of blood pressure acting on the chemoreceptors of the arch of the aorta and the carotid bodies may produce respiratory arrest; this effect, which is called an adrenaline apnœa, has not been demonstrated in Man. An excessive increase or decrease of intrapulmonary pressure may produce cessation of breathing. This is a vagal effect, initiated by interoceptive impulses in the lung substance; in animals, the stimulation of the central cut end of the vagus nerve may produce a vagus apnœa. If the tension of carbon dioxide in alveolar air, and consequently in arterial blood, is lowered by vigorous artificial respiration, breathing ceases and a carbon dioxide apnœa results. The initiation of controlled respiration, which is used so extensively in modern anæsthetic practice, depends upon an apnœa produced by artificial respiration and the use of moderate positive pressure. The respiratory centre may also be depressed by anæsthetic overdose and finally, during curarisation all skeletal muscles—including the crural fibres of the diaphragm—may be paralysed.

During anæsthetic maintenance in an adequately oxygenated subject unable to react to external stimulus and not exposed to extremes of intrapulmonary pressure, respiratory arrest may, therefore, be due to a *carbon dioxide apnœa* and/or *to anæsthetic overdose* and/or *to excessive curarisation.* A carbon dioxide apnœa is rapidly corrected by artificial respiration with an oxygen

atmosphere containing more than 6 per cent. of carbon dioxide. Respiratory depression produced by overdose with inhalation anæsthetics is corrected by artificial respiration with an oxygen atmosphere, for this prevents anoxia and produces the rapid excretion of the anæsthetic and relief from overdose, with a return of spontaneous breathing. With non-volatile blood-borne anæsthetics, the same treatment offers the best hope of the support of the cardiovascular system with, in turn, the excretion of the anæsthetic and eventual relief from overdose. In a conscious subject, and during anæsthesia when anoxia and carbon dioxide apnœa are avoided and the respiratory centre is not depressed by anæsthetic overdose, muscle tone returns in overcurarised crural fibres of the diaphragm in ten to twenty minutes. It has been shown that, when the respiratory centre is not depressed, curarisation of the diaphragm has no effect upon the impulses which are recordable at the central cut end of the phrenic nerve. This period of ten to twenty minutes represents the time taken in a normal subject to accumulate sufficient ACh, released by the impulses from the respiratory centre to displace and replace d-tubo-curarine chloride at the neuromuscular junction of the crural fibres of the diaphragm. In the absence of other factors, the time *taken to accumulate an effective quantum of ACh at the neuro*muscular junction of the crural fibres of the diaphragm can be reduced to thirty to sixty seconds by the intravenous injection of 2 mgs. of prostigmine.

When cyclopropane is used in clinical anæsthetic practice it is sometimes difficult to decide whether respiratory arrest is produced by anæsthetic overdose or by overcurarisation, and *in adequately atropinized subjects* the intravenous injection of prostigmine is employed as a clinical test to differentiate between these two factors. Thus, artificial respiration is performed with an oxygen atmosphere containing more than 6 per cent. of carbon dioxide and when it is estimated that a possible carbon dioxide apnœa has been corrected, 2 mgs. of prostigmine are injected intravenously. If anæsthesia is to the level of complete sensory loss or deeper, prostigmine will have no effect upon skeletal muscles other than the crural fibres of the diaphragm, for efferent impulses to these muscles from the higher centres are minimal or have entirely ceased. If the respiratory centre is active, and if impulses are in

fact passing normally to the neuromuscular junction of the crural fibres of the diaphragm, this anti-cholinesterase permits the rapid accumulation of sufficient ACh to displace and replace the d-tubo-curarine chloride fixed at this site and breathing will recommence within thirty to sixty seconds after the injection of prostigmine, without however, any return of muscle tone in the other skeletal muscles of the body. The return of spontaneous respiration is first indicated by a slight downward movement of the thyroid cartilage, which soon becomes a definite tracheal tug as the volume of lung ventilation gradually increases in amplitude. If, however, the respiratory centre is depressed by anæsthetic overdose, ACh is not released at the neuromuscular junction of the diaphragm, and prostigmine can produce no result. In this instance, artificial respiration with an oxygen atmosphere must be continued until anæsthetic overdose has been corrected.

There is one further possible cause of anoxia during curarisation, and it is the respiratory obstruction caused by bronchospasm. The smooth muscle of the bronchi receive dilator fibres from the sympathetic system and constrictor fibres from the parasympathetic system. Afferent impulses producing bronchospasm are initiated in many parts of the body and in the bronchial tract itself; when appropriate local stimulus, such as the presence of an endotracheal catheter, is permitted to act during light blood-borne anæsthesia, bronchospasm may occur.

It is known that crude curares produce bronchospasm. Dixon and Brodie (1903) observed that crude curarines contain a substance which caused the bronchial muscles to constrict. Landmesser (1947) stated that seven out of ten dogs showed bronchiolar constriction after the injection of 0·3 mgs. of d-tubo-curarine. West (1938) using calabash-curarine (the purity of which he had reason to doubt) reported several cases of broncho-spasm in humans during the less intense degrees of curarisation used in the treatment of tetanus and other spastic states. Gray and Halton (1948) reported only one case of bronchospasm during curarisation in 2,500 human subjects, and this case, "a very bad asthmatic, bronchoscoped when thiopentone was the only anæsthetic used." Whitacre and Fisher (1945) reported two cases in whom surgical stimulation produced bronchospasm. In the first instance, bronchospasm disappeared when a sufficient depth of

anæsthesia had been achieved; in the second, an increase in the degree of curarisation produced the same result. Prescott (1946) believed bronchospasm to be a danger in man if the subject is conscious, or lightly anæsthetised, or if small doses of d-tubocurarine chloride are used. Para-sympathetic effects are sometimes seen during electrical convulsive therapy in adequately curarised (30 milligrams of d-tubo-curarine chloride), under-atropinized, conscious, or lightly anæsthetised subjects. These effects do not occur when the subject is adequately atropinized; in spite of occasional under-atropinization, bronchospasm has not been seen in 2,500 such treatments. In subjects curarised during blood-borne anæsthesia for surgical procedures, the writer has never seen the slightest evidence of bronchospasm. Local stimulation was avoided in his cases, for an endotracheal catheter was seldom used during curarisation (which was always intense); subjects were always adequately atropinized and anæsthesia was maintained throughout at the level of complete sensory loss. When it was necessary to use an endotracheal catheter, local stimulation was abolished with a local anæsthetic spray to the nasopharynx and the glottic area, and early curarisation was occasionally employed to ablate the glottic spasm occasionally encountered during anæsthetic induction. The writer's experience during curarisation for electrical shock therapy and for surgical procedures leads him to believe that pure curarine, viz. d-tubo-curarine chloride, does not produce bronchospasm, and that the possibility of this para-sympathetic effect is eliminated if an adequately atropinized subject is maintained at the level of complete sensory loss The importance of an adequate level of anæsthetic depression during curarisation seems to be stressed by the evidence already discussed, which indicates that the para-sympathetic entities of the hypothalamus recover during blood-borne anæsthesia before its sympathetic entities In this instance, para-sympathetic over-action, including bronchospasm, might well occur in the presence of appropriate stimulation as soon as the anterior and medial hypothalamic nuclei have recovered, and before the posterior and lateral hypothalamic nuclei have regained their functional activity.

Clinical evidence, which is now very extensive, leads the writer to conclude *that pure d-tubo-curarine chloride does not produce bronchospasm* Bronchial constriction may, however, occur during

curarisation when appropriate stimulation is permitted to act during light anæsthesia; the action of such stimuli is effectively prevented by anæsthesia to the level of complete sensory loss. *It can be concluded that d-tubo-curarine chloride in clinical doses inhibits the transmission of nerve impulses to the striated muscles of respiration, and that this is its only action on the respiratory system in Man.* During clinical curarisation, oxygen lack is a very real danger, but anoxia can be effectively prevented by the insufflation of an atmosphere containing oxygen at an adequate partial pressure.

From time to time, it has been suggested that curarine has narcotic properties. Thus, Feitelberg and Pick (1942), and Pick and Unna (1945), reported that curarine abolished cortical potentials in frogs, independently of its paralysing action at the neuromuscular junction of skeletal muscles. This was confirmed with d-tubo-curarine chloride by Wintersteiner and Dutcher (1943). Stern and Rothlin (1918) reported increased restlessness and reflex activity when curarine enters the fourth ventricle, and Von Euler and Wahland (1941) stated that the intercisternal injection of curarine at first stimulated and then produced respiratory and vasomotor paralysis of long duration. Blume (1934) and others have shown that a strychnine effect is produced when curarine is applied directly to the spinal cord. None of these observations, however, are applicable in clinical anæsthetic practice, for the results obtained in amphibia are not reliable evidence of the behaviour of mammals, and the blood concentration of d-tubo-curarine chloride in clinical practice never approaches the concentration achieved locally in such experiments. *In vitro* experiments by Warburg showed that curarine had no effect upon the oxygen consumption of the cerebral cortex of mice. Featherstone and Gross (1947) observed, when pyruvate was used as the substrate, that d-tubo-curarine chloride had no effect upon the oxygen consumption of minced rat's brain.

Cushny (1928) and Poulssons (1938) stated that curarine does not affect the peripheral terminations of the sensory nerves and Kellgrew, McGowan and Wood (1946) reported that pain stimulation curves that are positively affected by small doses of morphia, are unaffected by curarisation. The writer has observed 243 unanæsthetised human subjects during curarisation to the

degree of diaphragmatic paralysis. He *believes that if anoxia is* avoided consciousness is not lost, for in general the subjective symptoms of these subjects were as follows:

They *first complained of furry vision,* which *became* more blurred as diplopia increased. The eyelids felt heavy and soon became paralysed, but if they were raised by the observer, light was perceived, and the pupils dilated and constricted reflexly to light. Then the lower jaw felt heavy, the subject complaining of tightness of the throat, and the voice became husky. Hearing was unaffected, smell was relatively accurate and touch and pressure were interpreted as such. In subjects who have some idea of the action of curare, intense mental stress amounting to panic may be experienced at this point, but in many of the writer's patients, to whom the injection of d-tubo-curarine chloride was " just another injection," this fear was absent. Oxygen lack, however, produced rapid loss of consciousness and complete sensory loss These *observations are in keeping with the results* of Whitacre and Fisher (1945), who unsuccessfully attempted to produce analgesia in adequately oxygenated human subjects with repeated small doses of curarine short of diaphragmatic paralysis Finally, there is the personal experience of Dr F. Prescott (1946) and Dr Scott M. Smith (1947) who both remained conscious when curarised to a degree comparable with that of clinical anæsthetic practice. Moreover, Prescott when fully curarised with 30 milligrams of d-tubo-curarine chloride, was conscious of considerable pain when adhesive strapping was torn from the hairy parts of his body. *It can be concluded that d-tubo-curarine chloride has no narcotic action*, and that if the central nervous system is depressed during curarisation in Man, this must be attributed to anoxia produced *by respiratory obstruction, and/or the* paralysis of respiratory muscles

The action of curare on the cardiovascular system has been *investigated by many observers.* There is little doubt that the intravenous injection of crude curarines depresses the cardiovascular system in keeping with the curine content of the particular sample, for curines are cardiac depressents. The slow intravenous injection of semi-crude curarines, such as intocostrin, produces little significant fall of blood pressure, but if larger doses are injected intravenously at a rapid rate, a precipitous fall of blood

pressure may occur, and when semi-crude curarines are injected into the carotid artery of experimental animals, death of the animal may occur almost coincident with the injection. Claude Bernard (1857) and others observed that the ability of the vagus to slow the heart could be abolished by curarine, but Bidder (1865) could not produce this effect. Observations made in clinical practice since the introduction of d-tubo-curarine chloride seem to confirm Bidder's view, but vagal inhibition does not occur in adequately atropinized subjects, even during the potent stimulation which occurs during electrical convulsive therapy. Ruskin, Ewalt and Dechard (1943) and Gray (1948) have shown that pure curarine in the dosage employed in clinical anæsthetic practice, fails to modify the electrocardiographic tracings of normal or abnormal human hearts, if anoxia is avoided, but Harroun, Becket and Fisher (1947) reported a slight electrocardiographic change which resembled that of a high serum potassium. Gaskell (1878-79) and others observed no effects upon the blood vessels with crude or semi-crude curarines and this view coincides with the observations made with pure d-tubo-curarine. Hence it can be concluded that pure d-tubo-curarine chloride in clinical dosage modifies neither cardiac output, nor peripheral resistance, and, in consequence, should not influence blood pressure. The same is found in clinical anæsthetic practice, for even when d-tubo-curarine chloride is injected rapidly in clinical doses, there is no significant fall of blood pressure. Larger doses of curarine, however, produce a material fall of blood pressure owing to the depression of the autonomic ganglia Still larger doses inhibit vagal action, and the heart rate is augmented; but neither the myocardium nor the conducting mechanism of the heart are affected. Dale and Laidlaw (1911) state that the vagal mechanism recovers in about fifteen minutes.

Pearlstein and Weinglass (1944) investigated the effect of prolonged curarisation in dogs. In general, they found that bradycardia and cardiac arrythmias developed after about three hours' curarisation. This condition was eventually followed by tachycardia, and syncope occurred after a period of curarisation which varied in duration from three to forty-five hours. In each instance, a dilated heart and congestion of the viscera were the only abnormalities found post mortem. They attributed this

cardiovascular collapse to a cardiac toxin, and they concluded that potassium was not the responsible agent, for they observed that the serum potassium of dogs was unaffected after six hours' curarisation. Neither acetylcholine nor the anti-cholinesterase action of intocostrin proved to be the toxic agent, and no protection was afforded by the continuous administration of atropine, pilocarpine, or ergotamine tartrate; on the contrary, administration of these drugs accelerated the onset of cardiac failure.

During clinical anæsthesia, when d-tubo-curarine chloride is used in clinical dosage, bradycardia and cardiac arrythmias followed by tachycardia, fall of blood pressure, and fatal cardiac failure may be the sequence of events which occurs when uncontrolled anoxia is permitted to act. But in an adequately oxygenated subject, the same sequence may follow a period of curarisation which may be as short as forty-five minutes in a subject with hyperpiesis and as long as two hours in a normal subject. In an adequately oxygenated subject, cardiovascular collapse of this nature can be prevented, or its development halted, by the timely administration of intravenous fluid. Plasma or normal saline is effective for short periods of time, *i.e.* for about thirty minutes; whole blood will effectively prevent the onset of this sequence of cardiovascular collapse for long periods of time, and will render curarisation for a period of five hours a safe clinical procedure. The clinical effectiveness of the intravenous administration of whole blood in preventing or aborting this form of cardiovascular collapse indicates that it has its origin not in cardiac toxin, *but in the* gradual fall of cardiac output, caused by the progressive diminution of the volume of venous blood returned to the right heart.

The return of venous blood to the right heart normally depends upon muscle movement, muscle tone, and the aspirating effect of negative intrapleural pressure produced on inspiration. During [illegible] The [illegible] curarisation employed in clinical anæsthetic practice, degregated by muscle movement and muscle tone in all skeletal abolition of injecn crural fibres of the diaphragm—combines with cles—except the em in hess of negative intrapleural pressure, produced educed effective ines eathing which accompanies this degree of he shallow mi-c ultimately reduces the volume of venous blood sation, and so bre ght heart to a critically low level. When this venitput is reduced, and the vicious circle of fall of

blood pressure and anoxia is initiated, and rapidly produces fatal cardiac failure unless halted by the timely intravenous administration of whole blood.

It can be concluded that d-tubo-curarine chloride in the dosage employed in clinical anæsthetic practice has no specific action on the cardiovascular system, and that the cardiovascular collapse occurring during prolonged curarisation in clinical anæsthetic practice may be attributed to loss of muscle tone in skeletal muscles. The retention of vasomotor control during clinical curarisation is in contrast to the paralysis of vaso-constrictor nerves, which occurs during spinal anæsthesia and in clinical practice, when venous return is adequate; the blood pressure is affected only inasmuch as the level of anæsthetic depression and the degree of curarisation has reduced the metabolic rate of the subject.

Experimental data of a specific action of pure curarine, on body metabolism as a whole or on individual organs and systems, are scanty, but much clinical evidence has been acquired in Man during the past five years. Such as it is, this evidence suggests that d-tubo-curarine chloride in clinical dosage exerts no specific action on metabolism or on organs and systems other than striated muscle; any modification of their functional activity which occurs during clinical curarisation may be attributed to the results of loss of muscle tone in skeletal muscles.

In conscious curarised subjects, the body temperature is maintained within normal limits. The paralysis of skeletal muscles reduces the activity of the body to a resting level, but there is no evidence that curarisation reduces body metabolism below its resting rate; and although the paralysis of skeletal muscle might be expected to diminish heat production, the central nervous system is not depressed, the hypothalamus is intact and active, and vasomotor tone is unaffected. It follows that the intact hypothalamus effectively regulates heat loss and heat production in the body taken as a whole; in the absence of other factors, body temperature is maintained within normal limits. When, however, curarisation is combined with blood-borne anæsthesia, the subject becomes poikilothermic as soon as the level of anæsthetic depression is sufficient to inhibit the functional activity of the hypothalamus.

Colasanti (1878) observed no difference in the oxidation of

normal and curarised muscle, and it has been observed that curarised muscle responds in a normal manner to the application of a potassium salt. Leulier and Vanhemis (1935) and McIntyre and King (1944) reported that curarised muscle contained less potassium than normal controls, but Pearlstein and Weinglass (1944) observed no increased in the serum potassium of dogs after six hours' curarisation. During clinical anæsthetic practice, the writer has observed no increase in the serum potassium in Man after curarisation lasting from one to three hours. When this is added to the fact that appropriate prostigmine very rapidly abolishes curarisation in normal skeletal muscles, it can be concluded that neither the oxidation processes, the potassium content of skeletal muscles, or the synthesis and release of acetylcholine, but only its fixation, is affected during curarisation.

Alam *et al* (1939) reported the release of a histamine-like substance from normal and denervated curarised muscle. The bronchospasm produced by crude curares has been attributed to a histamine-like substance, but bronchospasm does not occur with pure curarine in the absence of appropriate stimulus. Schild and Gregory have shown that d-tubo-curarine chloride can liberate histamine from skeletal muscle, but Macintosh and Paton (1949) observed that 0 6 mg./kg. was the smallest dose of d-tubo-curarine chloride to produce a depressor effect, and *it can be concluded that d-tubo-curarine chloride in clinical dosage does not liberate histamine in significant amounts.* Neither in conscious nor in anæsthetised subjects has one been able to elicit the triple skin response which would indicate that significant amounts of histamine had been liberated during clinical curarisation.

In clinical dosage, d-tubo-curarine chloride does not affect the functional activity of the autonomic ganglia, and the smooth muscles of the stomach, intestines, bladder, and other viscera retain their tone during clinical curarisation in conscious subjects Dawkins (1947) has reported ileus in the post-anæsthetic period after clinical curarisation, but this may be due to anæsthesia or to other causes peculiar to the surgical interference, and/or the post-operative treatment. The writer has not, to date, encountered ileus following anæsthesia when d-tubo-curarine chloride was used in clinical dosage. Moreover, curarine in larger doses abolishes the nicotine action of acetylcholine, but has little or no

effect upon is muscurine action, and, even so, smooth muscle reactions and secretions are generally little altered.

Pavlow (1878) and others, using semi-crude curares, concluded that salivation increased and that the volume of flow varied as the degree of curarisation; but McIntyre (1947) states that in short periods of curarisation there is no significant increase of salivation. In under-atropinized curarised subjects, the very intense stimulation produced by electrical convulsive therapy results in excessive salivation. During curarisation in an adequately atropinized and lightly anæsthetised subject, local stimulation (produced by an airway or by the passage of an endotracheal tube) results in salivation of the same order as might occur in an uncurarised subject in comparable circumstances: but in a curarised subject, during anæsthesia maintained at the level of complete senory loss, excessive salivation has never been encountered. It has been observed by Cole *et al* (1947) that gastric secretion is unaffected during curarisation. Bernstein (1896) and Gayet and Guillaume (1934) concluded that curarine augments the external secretion of the pancreas, but Goetzner (1920) did not observe this effect. No evidence is available of the internal secretion of the pancreas during curarisation, but many observers have reported hyperglycæmia during curarisation with crude, semi-crude and pure samples of curarine. Langendroff (1886-87) observed glycosuria in curarised dehepatised frogs, but Geiger (1931-33) could not confirm these observations; his work, and the work of Bock and Hoffmann (1874), Dock (1872) and many others, make it clear that the rise of blood sugar and the glycosuria, which occurs during curarisation, is due to liver glycogenolysis. This glycogenolysis has been attributed to the specific action of curarine on the liver, but most authorities agree that it is due to the increased secretion of adrenaline produced by psychic factors and/or to anoxia. It can be controlled by the injection of appropriate insulin, but this is not an indication of insulin deficiency produced by curarine, for the residual hyperglycæmia of a given level of anæsthetic depression is not increased when d-tubo-curarine chloride is injected in clinical dosage, if anoxia is avoided. Pure curarine appears to have no specific action on the liver itself, for, in clinical practice curarisation in the presence of liver inefficiency has been found to be a safe clinical procedure.

In clinical dosage, neither uterine nor renal function is affected during curarisation, but there is a diminished secretion of urine with a compensatory increased secretion on recovery. This diminished urinary secretion is independent of the blood pressure and can be attributed, like the oliguria of natural sleep and anæsthesia, to the diminished activity of the body during curarisation. As in natural sleep and anæsthesia, so during curarisation, this diminished urinary secretion is accompanied by a retention of non-protein nitrogen, and the rapidity with which non-protein nitrogen accumulates in circulating blood is determined by the degree of oliguria and the rate of body activity. Dobozy (1940) observed that nephrectomised frogs died in five days, while curarised nephrectomised frogs survived for eight days, and this indicates that curarisation lowers the activity of the body and, in turn, the rate of accumulation of N.P.N.

The evidence presented indicates that d-tubo-curarine chloride in the dosage used in clinical practice has *one specfic action and one specific action only*, viz. that of inhibiting the action of ACh at the neuromuscular junction of skeletal muscle. It suggests that pure d-tubo-curarine chloride has *no side-actions whatsoever*, and that the deleterious effects which may follow its use in clinical anæsthetic practice, anoxia and deficient venous return, *are directly attributable to its dominant action which is the reversible inhibition of muscle tone in skeletal muscles.* This conclusion goes far to substantiate the view of earlier observers that curarine is the most purely elective drug known to pharmacologists. And it is clear that it is the complete absence of side-actions which makes d-tubo-curarine chloride such an exceedingly safe and flexible adjuvant to clinical anæsthetic practice.

When d-tubo-curarine chloride is administered intravenously, the degree of curarisation varies as the dose injected. In mice, rats and rabbits, Collier, Paris and Woolf (1948) observed that the intravenous administration of about half the minimal effective dose of d-tubo-curarine chloride produced no loss of muscle tone; when this same dose was repeated after an interval of about fifteen minutes, muscle tone was reduced to about 95 per cent. of that produced by a single effective dose. The existence of this threshold is in keeping with the " all-or-none " character of the response of single nerve fibres, and the summation of sub-liminal

depression of neuromuscular transmission with d-tubo-curarine chloride is also consistent with this law.

Clinical observations of the action of d-tubo-curarine chloride in Man, however, shows that there is a very considerable variation in the intravenous dose of d-tubo-curarine chloride required to produce full curarisation. *There is evidence to indicate that the dominant factor determining the effective intravenous dose of d-tubo-curarine chloride, is the ability of the particular subject to synthesise and release ACh at the neuromuscular junction of skeletal muscles.*

It is observed that 30 milligrams of d-tubo-curarine chloride is required to produce diaphragmatic paralysis in a healthy, conscious, or lightly anæsthetised subject weighing about ten stones. In such a subject the synthesis of ACh is normal, and, since he reacts to external stimulation, ACh is released in normal quanta at the neuromuscular junction of skeletal muscles. If, however, the same subject be anæsthetised to the level of complete sensory loss, the intravenous injection of ten milligrams of d-tubo-curarine is often sufficient to produce diaphragmatic paralysis, and this dose will invariably produce loss of muscle tone in the intercostal muscles, and the sternocostal fibres of the diaphragm. In this anæsthetised subject, the synthesis of combined ACh is normal, but the diminution in the intensity of efferent impulses reaching peripheral motor nerve endings reduces the amount of ACh released at the neuromuscular junction of skeletal muscles to small proportions. Consequently, the quantum of d-tubo-curarine chloride which must be concentrated at the neuromuscular junction of skeletal muscles to displace and replace this minimal amount of ACh is correspondingly reduced. And finally, if d-tubo-curarine chloride was inadvertently administered to a subject with myasthenia gravis, an intensely powerful effect would be produced with a very small intravenous dose—an effect that might even be irreversible. Harvey and Lilienthal (1941) concluded that the loss of muscle tone in subjects with myasthenia gravis was due either to the presence of a hypothetical curare-like substance in the blood of these subjects, or to a lowered quantum of ACh at the neuromuscular junction of the skeletal muscles produced by excess of cholinesterase, or by the deficient synthesis of combined ACh by the myasthenic muscles. Excess of cholinesterase had not been found in myasthenic subjects,

In clinical dosage, neither uterine nor renal function is affected during curarisation, but there is a diminished secretion of urine with a compensatory increased secretion on recovery. This diminished urinary secretion is independent of the blood pressure and can be attributed, like the oliguria of natural sleep and anæsthesia, to the diminished activity of the body during curarisation. As in natural sleep and anæsthesia, so during curarisation, this diminished urinary secretion is accompanied by a retention of non-protein nitrogen, and the rapidity with which non-protein nitrogen accumulates in circulating blood is determined by the degree of oliguria and the rate of body activity. Dobozy (1940) observed that nephrectomised frogs died in five days, while curarised nephrectomised frogs survived for eight days, and this indicates that curarisation lowers the activity of the body and, in turn, the rate of accumulation of N.P.N.

The evidence presented indicates that d-tubo-curarine chloride in the dosage used in clinical practice has *one specfic action and one specific action only*, viz. that of inhibiting the action of ACh at the neuromuscular junction of skeletal muscle. It suggests that pure d-tubo-curarine chloride has *no side-actions whatsoever*, and that the deleterious effects which may follow its use in clinical anæsthetic practice, anoxia and deficient venous return, *are directly attributable to its dominant action which is the reversible inhibition of muscle tone in skeletal muscles* This conclusion goes far to substantiate the view of earlier observers that curarine is the most purely elective drug known to pharmacologists. And it is clear that it is the complete absence of side-actions which makes d-tubo-curarine chloride such an exceedingly safe and flexible adjuvant to clinical anæsthetic practice.

When d-tubo-curarine chloride is administered intravenously, the degree of curarisation varies as the dose injected. In mice, rats and rabbits, Collier, Paris and Woolf (1948) observed that the intravenous administration of about half the minimal effective dose of d-tubo-curarine chloride produced no loss of muscle tone; when this same dose was repeated after an interval of about fifteen minutes, muscle tone was reduced to about 95 per cent. of that produced by a single effective dose. The existence of this threshold is in keeping with the " all-or-none " character of the response of single nerve fibres, and the summation of sub-liminal

subjects with myasthenia gravis, d-tubo-curarine chloride is absolutely contra-indicated. It is the duty of the anæsthetist to learn to recognise a myasthenic subject during his pre-anæsthetic investigations.

It can be concluded that *the degree of curarisation in man varies as the intravenous dose of d-tubo-curarine chloride, but that the effective intravenous dose of d-tubo-curarine chloride in the particular subject is determined by his ability, at the time of this injection, to release ACh at the neuromuscular junction of the skeletal muscle.*

The duration of action of d-tubo-curarine chloride, and di-methyl ether of d-tubo-curarine iodide in mice, rats and rabbits, has been observed by Collier, Paris and Woolf (1948) to bear an approximate linear relationship to the logarithm of the dose over a greater part of the clinical dosage range. And the duration ot action of these curarising drugs for unit increase of the logarithm of the dose was found to be an inverse function of the rate of elimination, whether by destruction or excretion.

The mechanism of the clearance of d-tubo-curarine chloride from circulating blood, and its excretion from the body has not yet been determined in Man, and the method of its elimination from the body appears to vary in different species. In frogs and rabbits, the kidneys appear to be the obligatory route of its excretion. Bidder (1865) succeeded in curarising four successive frogs by injecting the urine of the first curarised frog into the second frog, and so on; Voisin and Lionville (1920) successfully repeated the experiment in rabbits. In experiments on animals with Eck's fistula, Boehm concluded that the liver plays a minor rôle in the excretion of curare. On the other hand, Edwards (1948) states that d-tubo-curarine chloride is excreted by dogs partly by the kidneys, partly after detoxication in the liver; this appears to be supported by the observation of Collier, Paris and Woolf (1948) who observed in rodents that litigation of the renal arteries and veins, prior to the intravenous injection of d-tubo-curarine chloride, increased the duration of its action, but did not prevent recovery of muscle tone. Everett (1948), however, reported that neither double nephrectomy, nor the removal of 70 - 90 per cent. of the liver and kidneys, prolonged the duration of action of d-tubo-curarine chloride in rats, implying that

and the hypothetical curare-like substance has not to date been identified. Burn (1948) is of the opinion that there is an inability to synthesise and store combined ACh in these subjects. If the synthesis of combined ACh was faulty, efferent impulses would effect the release of sub-normal amounts of ACh at the neuromuscular junction of skeletal muscles and, moreover, repeated demands would soon exhaust the store of combined ACh present in the muscle cells. But the affected skeletal muscles of a myasthenic subject are hypersensitive to released ACh. The accumulation of even small quanta of ACh at the neuromuscular junction of these muscles produced by prostigmine therefore causes a temporary return of muscle tone; the ability of the myasthenic muscle to synthesise and store combined ACh will in turn determine the duration of this remission. Since the inhibition of ACh by d-tubo-curarine chloride is an adsorption-displacement mechanism, the hypersensitiveness of myasthenic muscles to ACh can do nothing to influence the effective dose of d-tubo-curarine chloride *which depends solely upon the quantum of ACh which must be displaced* and replaced at the neuromuscular junction of these muscles. And the tiny effective dose of d-tubo-curarine chloride in myasthenic subjects can be attributed solely to the very small amount of ACh which can accumulate at the neuromuscular junction of the skeletal muscles of these subjects. Moreover, because repeated demands soon exhaust the meagre store of combined ACh and because the rate of synthesis of combined ACh is faulty, it may be difficult or even impossible to accumulate sufficient ACh at the neuromuscular junction of the skeletal muscles of a myasthenic subject to displace d-tubo-curarine chloride from its fixation at this site: in this event, its action is to all intent and purpose irreversible. *Reference to Figure 15 indicates that a cause of the faulty synthesis* of combined ACh in myasthenic subjects might well be sought in abnormal carbohydrate metabolism and/or a deficiency in the specific protein—the enzyme choline acetylase—in the myasthenic muscle.

Clinical experience has shown that the average effective dose of d-tubo-curarine chloride in a healthy conscious, or lightly anæsthetised subject, is about 2½ milligrams per stone of body weight, and about 1 milligram per stone of body weight in healthy subjects anæsthetised to the level of complete sensory loss. In

subjects with myasthenia gravis, d-tubo-curarine chloride is absolutely contra-indicated. It is the duty of the anæsthetist to learn to recognise a myasthenic subject during his pre-anæsthetic investigations.

It can be concluded that *the degree of curarisation in man varies as the intravenous dose of d-tubo-curarine chloride, but that the effective intravenous dose of d-tubo-curarine chloride in the particular subject is determined by his ability, at the time of this injection, to release ACh at the neuromuscular junction of the skeletal muscle.*

The duration of action of d-tubo-curarine chloride, and di-methyl ether of d-tubo-curarine iodide in mice, rats and rabbits, has been observed by Collier, Paris and Woolf (1948) to bear an approximate linear relationship to the logarithm of the dose over a greater part of the clinical dosage range. And the duration of action of these curarising drugs for unit increase of the logarithm of the dose was found to be an inverse function of the rate of elimination, whether by destruction or excretion.

The mechanism of the clearance of d-tubo-curarine chloride from circulating blood, and its excretion from the body has not yet been determined in Man, and the method of its elimination from the body appears to vary in different species. In frogs and rabbits, the kidneys appear to be the obligatory route of its excretion. Bidder (1865) succeeded in curarising four successive frogs by injecting the urine of the first curarised frog into the second frog, and so on; Voisin and Lionville (1920) successfully repeated the experiment in rabbits. In experiments on animals with Eck's fistula, Boehm concluded that the liver plays a minor rôle in the excretion of curare. On the other hand, Edwards (1948) states that d-tubo-curarine chloride is excreted by dogs partly by the kidneys, partly after detoxication in the liver; this appears to be supported by the observation of Collier, Paris and Woolf (1948) who observed in rodents that litigation of the renal arteries and veins, prior to the intravenous injection of d-tubo-curarine chloride, increased the duration of its action, but did not prevent recovery of muscle tone. Everett (1948), however, reported that neither double nephrectomy, nor the removal of 70 - 90 per cent. of the liver and kidneys, prolonged the duration of action of d-tubo-curarine chloride in rats, implying that

mammals without liver or kidney function can detoxicate d-tubo-curarine chloride. These observations show that d-tubo-curarine chloride is excreted unchanged in the urine by the kidneys of frogs and rabbits, and suggests that in mammals it may also be destroyed in the liver and perhaps in other tissues throughout the body.

Prescott *et al* (1946) state that d-tubo-curarine chloride is excreted unchanged in the urine by the kidneys in Man, and Cullen (1944) and Griffith (1945) assert that it is also detoxicated by the liver. Clinical experience is now sufficiently extensive to show *that neither renal or liver inefficiency increases the intensity or duration of action of d-tubo-curarine chloride administered to human subjects in clinical dosage.* This tends to confirm Everett's inference that d-tubo-curarine chloride may be detoxicated or destroyed in other tissues throughout the body. But there may be factors other than excretion and/or detoxication which influence the duration of loss of muscle tone in skeletal muscles in response to standard doses of d-tubo-curarine chloride. Clinical observations in Man curarised to a given level under varying circumstances, indicates that the rapidity with which a certain critical concentration of ACh accumulates at the neuromuscular junction of skeletal muscles is probably the most important factor in determining the duration of action of a given effective intravenous dose of d-tubo-curarine chloride

Thus, Prescott (1946) reports that muscular power had completely returned thirty minutes after he had been curarised to the level of diaphragmatic paralysis with 30 milligrams of d-tubo-curarine chloride given intravenously.

In a series of 243 conscious subjects curarised to the level of diaphragmatic paralysis with 30 milligrams of d-tubo-curarine chloride and then given electrical convulsive therapy (E.C.T.), complete return of muscle power occurred within 20 - 30 minutes of the completion of treatment; one of them, a woman aged sixty-five years, was observed to walk to the bathroom twenty minutes after completion of treatment.

In 500 subjects lightly anæsthetised with 0·5 grams of pentothal and then curarised to the same level with 30 milligrams of d-tubo-curarine chloride for the same purpose, muscular power completely returned within 20 - 30 minutes.

The factors common to these three series of cases are that

30 milligrams of d-tubo-curarine chloride produced diaphragmatic paralysis; that these conscious or lightly anæsthetised subjects could react to external stimulation, and so effect the release of ACh at the neuromuscular junction of skeletal muscles; and that muscular recovery was complete within 20 - 30 minutes. This period therefore represents the time taken by a subject who can react to external stimulus, to accumulate sufficient ACh to displace d-tubo-curarine chloride from its fixation at the neuromuscular junction of skeletal muscle and replace it at the site with ACh.

When, in a subject who can react to external stimulation, the rate of accumulation of ACh at the neuromuscular junction of skeletal muscle is accelerated by the use of an anticholinesterase, the return of muscular power is hastened. Thus, in 1,550 subjects lightly anæsthetised with 0 5 grams of pentothal, given atropine gr. 1/50th and curarised with 30 milligrams of d-tubo-curarine chloride to the level of diaphragmatic paralysis, E.C.T. was immediately followed by 2½ milligrams of prostigmine injected intravenously. and in this series of cases, muscular power returned within 3 - 5 minutes of the intravenous injection of anticholinesterase. In this series, therefore, 3 - 5 minutes represents the time taken to accumulate sufficient ACh at the neuromuscular junction of skeletal muscles to displace d-tubo-curarine chloride from this, the site of its fixation, and to replace it at this site with ACh.

But loss of muscle tone in skeletal muscles can be maintained for as long as the accumulation of an effective concentration of ACh at the neuromuscular junction of skeletal muscle is prevented. Thus, in a large series of surgical cases, anæsthetised to the level of complete sensory loss, and curarised to the level of intercostal paralysis with 10 milligrams of d-tubo-curarine chloride, it is observed that this level of curarisation can be continued for up to five hours without the administration of additional d-tubo-curarine chloride, if the ability of the subject to react to external stimulation and so release ACh at the neuromuscular junction of skeletal muscles, is effectively prevented by the maintenance of anæsthesia to the level of complete sensory loss throughout.

Finally, the inability of the myasthenic subject to accumulate an effective concentration of ACh at the neuromuscular junction of his skeletal muscles may render the action of d-tubo-curarine chloride on such a subject completely irreversible.

Hence, it can be concluded that the duration of action of d-tubo-curarine chloride is determined solely by the duration of its fixation at the neuromuscular junction of skeletal muscle, and that the duration of its fixation in turn is determined by the quantum of ACh present at this site. In clinical anæsthetic practice, the intensity and duration of action of d-tubo-curarine chloride can be controlled at will, for, as long as the respiratory centre is functionally active, prostigmine in appropriate dosage will de-curarise the crural fibres of the diaphragm; curarisation to the level of intercostal paralysis, once established, can be prolonged for as long as anæsthesia to the level of complete sensory loss is maintained; and muscle tone will return in all skeletal muscles as soon as anæsthesia lighter than complete sensory loss permits ACh to accumulate in an effective quantum at the neuromuscular junction of skeletal muscles. *Thus any factor which retards the accumulation of ACh in effective quanta prolongs the duration of action of d-tubo curarine chloride and its duration of action is shortened by factors which hasten the accumulation of ACh.*

The results of wash-out experiments led the earlier observers to believe that curare was bound (fixed) very quickly and retained for a long period of time. They concluded that the action of curare ceased when its concentration in the tissues about the nerve endings fell, owing to the excretion of excess of curare from circulating blood by the kidneys.

An effective intravenous dose of d-tubo-curarine chloride produces full curarisation in Man within two to three minutes, and its fixation is without doubt rapid. The duration of its fixation, and in turn the duration of its action in Man, may be relatively short, or it may be prolonged for a long period of time, in keeping with the ability or the inability of the subject to accumulate an effective concentration of ACh at the neuromuscular junction of skeletal muscles. Thus, when healthy conscious or lightly anæsthetised subjects are curarised to the level of diaphragmatic paralysis with 30 milligrams of d-tubo-curarine chloride, the return of muscle tone in all skeletal muscles, except perhaps the extrinsic muscles of the eyes, is complete within 20-30 minutes. This behaviour indicates that a sufficient proportion of this 30 milligrams of d-tubo-curarine chloride is cleared from circulating blood by excretion and/or detoxication within 20 - 30 minutes to reduce its

concentration below that required to displace and replace the normal quanta of ACh at the neuromuscular junction of all skeletal muscles, except perhaps the extrinsic muscles of the eyes. These observations suggest that (a) the fixation of d-tubo-curarine chloride is loose in subjects in whom ACh is released in normal quanta, and (b) the clearance of unfixed d-tubo-curarine chloride by excretion and/or detoxication is a dominant factor in determining the duration of action of d-tubo-curarine chloride in such subjects, and is fairly rapid. On the other hand, it has been seen in subjects anæsthetised to the level of complete sensory loss that 10 milligrams of d-tubo-curarine chloride produce curarisation to the level of intercostal paralysis and that this level of curarisation continues for as long as the release of ACh in normal quanta is prevented by the maintenance of anæsthesia to this level of depression. This implies that the fixation of d-tubo-curarine chloride is a firm one in the absence of ACh in effective quanta at the neuromuscular junction of skeletal muscles, and suggests that fixed d-tubo-curarine chloride is not subject to excretion and/or detoxication by the body. This conclusion is strengthened by the fact that in such subjects, as soon as anæsthesia is permitted to become lighter than complete sensory loss, ACh is again released and accumulates in sufficient quanta to effect the displacement and subsequent clearance by excretion and/or detoxication of this now unfixed d-tubo-curarine within a short period of time.

Hence, when a healthy subject anæsthetised to the level of complete sensory loss is curarised to the level of intercostal paralysis with 10 milligrams of d-tubo-curarine chloride, it can be supposed that a proportion of this 10 milligrams of d-tubo-curarine chloride is firmly fixed by specific muscle receptors, and produces loss of muscle tone in all skeletal muscles except the crural fibres of the diaphragm, and that the unfixed remainder of this d-tubo-curarine chloride is distributed between blood and tissues other than skeletal muscles, upon which it has no action. It can be assumed that the unfixed proportion is cleared from circulating blood and other tissues within 20 - 30 minutes, and that within 20 - 30 minutes the total d-tubo-curarine chloride content of the body has been reduced considerably below 10 milligrams—which can be regarded as the minimum threshold effective dose for such a subject. In the absence of released ACh the fixed d-tubo-

curarine chloride which remains continues to produce loss of muscle tone to the level of intercostal paralysis; but, when anæsthesia becomes lighter than complete sensory loss, fixed d-tubo-curarine chloride is rapidly displaced and replaced by ACh. Muscle tone rapidly returns and the presence of this small amount of now unfixed d-tubo-curarine chloride in the body is of no significance.

Some idea of the rate of clearance of this now unfixed d-tubo-curarine chloride can be gauged by the results obtained in clinical anæsthetic practice. Thus, when anæsthesia is permitted to become lighter than complete sensory loss, the tracheal tug disappears and muscle tone returns in the muscles of the trunk. If, however, anæsthesia can be deepened to the level of complete sensory loss within 3 - 5 minutes of the disappearance of the tracheal tug, the release of ACh ceases, and its rapid hydrolysis permits this unfixed d-tubo-curarine chloride to unite again with its muscle receptors, before it can be excreted and/or detoxicated in significant amounts: and the trunk muscles again lose their tone. If, however, more than about five minutes is allowed to elapse after the tracheal tug has disappeared, anæsthesia to the level of complete sensory loss no longer produces relaxation of the trunk muscles, and muscular relaxation can now be obtained only by an additional intravenous injection of d-tubo-curarine chloride, or by a deeper level of anæsthetic depression. It can be concluded, when a healthy subject anæsthetised to and maintained at the level of complete sensory loss is curarised to the level of intercostal paralysis, that the clearance of unfixed d-tubo-curarine chloride by excretion and/or by detoxication has no significant influence upon the duration of curarisation, and that fixed d-tubo-curarine chloride is not subject to excretion and/or detoxication by the body. Except in a myasthenic subject, it follows in clinical anæsthetic practice that recovery from curarisation should invariably be swift and trouble-free if anoxia is avoided.

Myasthenia gravis is the only contra-indication to the use of d-tubo-curarine chloride in clinical anæsthetic practice. Because of the faulty synthesis of combined ACh in these subjects, ACh is released at the neuromuscular junction of skeletal muscles in subnormal quanta; myasthenic subjects are consequently very susceptible to the action of d-tubo-curarine chloride. Moreover, evidence has been discussed which indicates that fixed d-tubo-

curarine chloride can be freed from muscle receptors only by the presence of an effective quanta of ACh at the neuromuscular junction of skeletal muscles. In myasthenic subjects, it may be impossible to achieve such a quantum of ACh at this site, and in this instance, the action of d-tubo-curarine chloride would be irreversible. McIntyre (1947) states that subjects do not develop a tolerance to the action of d-tubo-curarine chloride. This has been the author's experience also, for in a series of more than 300 subjects curarised prior to Electrical Convulsive Therapy (E.C.T.) or Continuous Electrical Narcosis Therapy (E.N.T.), in whom d-tubo-curarine chloride was administered to the level of diaphragmatic paralysis every second day for as few as six and as many as twenty consecutive intravenous injections, no hint of a growing susceptibility or a resistance to its action has been observed.

In clinical practice, d-tubo-curarine chloride is employed to obtain muscular relaxation during surgical procedures, and to protect the subject from the violent muscular contractions which occur when E.C.T. or E.N.T. is used in the treatment of certain psychiatric subjects.

The technique of its administration when used as an adjuvant to surgical anæsthesia has followed two distinct trends, which are as follows:

On the one hand, relatively light anæsthesia is produced and maintained with inhalation anæsthetics and/or with intravenous barbiturates such as pentothal, and 5 milligrams of d-tubo-curarine chloride are injected intravenously. If the subject shows no signs of susceptibility to d-tubo-curarine chloride after five minutes, an additional 15 to 25 milligrams of d-tubo-curarine chloride are then injected to produce curarisation to the level of intercostal paralysis. Because of the relatively light level of anæsthetic depression, ACh is released throughout at the neuromuscular junction of skeletal muscles and additional d-tubo-curarine chloride must be injected intravenously, secundum artem, to maintain curarisation at the level of intercostal paralysis.

On the other hand, myasthenic subjects having been excluded during the pre-anæsthetic examination, anæsthesia to the level of

complete sensory loss is produced and 1 milligram of d-tubo-curarine chloride per stone of body weight is then injected intravenously to produce curarisation to the level of intercostal paralysis. In this instance, however, ACh is not released at the neuromuscular junction of skeletal muscles in significant amounts, nor, therefore will additional d-tubo-curarine chloride be required to maintain this level of curarisation so long as anæsthesia to the level of complete sensory loss is continued.

In each instance, efficient curarisation is obtained. When anæsthesia lighter than complete sensory loss is maintained throughout, there is a minimal intensity of metabolic upset produced during anæsthetic maintenance and in the post-anæsthetic period; but, since the subject reacts in a reflex manner to external stimulation, reflexes designed to protect—cardiovascular reflexes, bronchial constriction, etc —*may react in an exaggerated manner and endanger the life of the subject.* When anæsthesia is maintained at the level of complete sensory loss throughout, the intensity of the metabolic upset produced is slightly increased; but complete safety is achieved, for the curarised subject, anæsthetised to this level of depression, fails to react to external stimulation. If it is accepted that the first duty of the anæsthetist is the production of a safe, efficient anæsthetic preparation, *it follows that anæsthesia to the level of complete sensory loss should be maintained throughout in subjects curarised for surgical procedures.*

Protection from physical trauma is the only possible reason for the use of d-tubo-curarine chloride during electrical convulsive therapy and continuous electrical narcosis therapy. And when d-tubo-curarine chloride is used as an adjuvant to these forms of psychiatric treatment, experience has shown that a number of conditions must be fulfilled if this adjuvant is not only to protect from physical trauma, but also to increase the safety of these forms of psychiatric treatment

Curarisation must be absolute and must reach the level of diaphragmatic paralysis if it is to protect adequately from physical trauma. Because emotionally disturbed subjects tend to elaborate a fresh set of symptoms around any frightening experience, and because it is desirable to inhibit sympathetic reactions, pentothal is administered intravenously to produce a pleasant anæsthetic induction to the level of anæsthetic sleep, when, as has been seen,

the posterior and lateral nuclear masses of the hypothalamus are depressed. It is also essential to inhibit para-sympathetic effects without at the same time inhibiting the release of ACh at the neuro-muscular junction of skeletal muscle, for a rapid return of muscle tone is required on the completion of treatment, and prostigmine as a means of obtaining the rapid return of muscle tone is useless unless ACh is released in normal quanta. Para-sympathetic effects can be inhibited without depressing the release of ACh at the neuro-muscular junction of skeletal muscle by the intravenous injection of atropine (gr. 1/50).

These various aims are achieved in a safe and a satisfactory manner by the following technique of administration, which has been evolved during more than 2,500 such psychiatric treatments with d-tubo-curarine chloride, in more than 380 subjects.

After eliminating the possibility of myasthenia gravis, the subject is prepared as for an anæsthetic. On the morning of treatment breakfast is withheld, except in diabetic subjects; immediately before treatment, dentures are removed, the bladder is emptied, etc. Treatment is carried out in the subject's own bed which is firm, without bed-boards. With the subject lying in the supine position with extended legs, and with a comfortable pillow, 0·4 to 0 5 grams of a 5 per cent. solution of pentothal are injected intravenously at a fairly rapid rate, viz. in about 15—20 seconds. This is immediately followed, through the same needle, by atropine, gr. 1/50, and 25—30 milligrams of d-tubo-curarine chloride mixed in the same syringe. A Phillips airway is then inserted and, while the skin of the temporal regions is being cleansed and the head pieces (terminals) are being adjusted in position, oxygen insufflation is carried out by the manual compression of the bag of a B.L.B. apparatus with a full face-piece, until the subject is flooded with oxygen and is a bright pink colour. The Phillips airway is now removed and a 2 inch length of stiff rubber hose of one inch diameter is placed between the molar teeth. The lower jaw is firmly supported against this rubber hose and the electrical shock is given. There is usually time to replace the rubber hose with a Phillips airway before the subject reacts to the electrical shock which, in an adequately curarised subject, is manifest by minor twitching of the face and limbs, and oxygen insufflation is again carried out with the B.L.B. apparatus.

In the first 250 treatments, prostigmine was not used to hasten recovery of muscle tone. Anoxia was prevented by the insufflation of oxygen and a tracheal tug appeared within 3-5 minutes of the cessation of muscle movement produced by the shock; the respiratory muscles recovered to the point of providing a volume of lung ventilation sufficient adequately to oxygenate the subject breathing atmospheric air in about 5-8 minutes, and muscle tone in all skeletal muscles was adequate to normal behaviour in about 20-30 minutes. Shortage of nursing staff, however, soon encouraged one to use prostigmine to hasten the return of muscle tone, and in the last 1,850 cases, 2½ milligrams of prostigmine have been injected intravenously as soon as the muscle movement produced by the shock has ceased. In this instance, a tracheal tug appears within 30-60 seconds of the intravenous administration of the prostigmine, and lung ventilation is sufficient to oxygenate adequately the subject breathing atmospheric air within about two minutes. Oxygen insufflation is seldom necessary, and muscle tone in all skeletal muscles is adequate to normal behaviour and the subject can be left unattended, in about five minutes. Precisely the same routine is used for E.N.T.

There is little doubt that E.C.T. can be safely carried out in normal subjects without d-tubo-curarine chloride when the physical stress of this form of treatment is effectively controlled. But quite apart from the risk of fractures, there are many aged and infirm psychiatric subjects, and those with myocardial degeneration, arteriosclerosis, etc., whose physical condition must deny them the benefit of E.C.T or E.N.T. unless they are protected by adequate curarisation. Such subjects can be safely submitted to E C.T. and E.N.T. if they are adequately curarised with d-tubo-curarine chloride. Thus, a depressed subject whose sixth cervical vertebra had been fractured fourteen months previously, was successfully given six E.C.T. treatments without incident while curarised with d-tubo-curarine chloride. Six subjects with old crush-fractures of thoracic vertebra, many senile subjects with myocardial degeneration, and subjects with hyperpiesis, have also been afforded this form of treatment by the use of d-tubo-curarine chloride. On the other hand, E.N.T. is considered to be a dangerous procedure even in normal subjects unless adequate curarisation is employed, for the tonic contraction of the respiratory muscles and those of the throat

and glottis—which occurs with E.N.T.—may render adequate oxygenation difficult or even impossible. Because of this, treatment is either insufficiently intense in the interests of adequate oxygenation or the pre-determined level of E.N.T. is maintained at the risk of anoxia. When curarised with d-tubo-curarine chloride, however, the absence of tone in the respiratory muscles and those of the throat and glottis permits adequate oxygenation with a B.L.B. apparatus, while the intensity of E.N.T. is maintained at any given level.

d-tubo-curarine chloride has proved to be a valuable adjuvant to E.C.T. and E.N.T., and to date more than 2,500 such treatments with d-tubo-curarine chloride have been carried out at the York Clinic. At first, cardiovascular para-sympathetic effects of a minor nature occasionally occurred, but no hint of bronchospasm has ever been observed. These para-sympathetic effects were soon eliminated when the importance of administering adequate atropine (gr. 1/50) at least five minutes before the intravenous injection of prostigmine was understood.

It can be concluded that d-tubo-curarine chloride is a safe, and a valuable adjuvant in clinical anæsthesia, and in the treatment of psychiatric subjects with E.C.T. and E.N.T.

References

1A. Alam, M., Anrep, G. V., Bassoum, G. S., Talaat, M., Weininger, E. (1939) *J. Physiol.* **95**, 148.
1. Bernstein, N O. (1896). *Arb. Physiol. Anst Leipzig.* **4**, 27.
2. Bernard, C. (1857). *Lecons sur les effets des substances toxiques.* (Paris.) p. 349
3. Bidder, F W. (1865). *Arch. Anat. Physiol. wiss Med* p. 337.
4. Blume, W. (1934). *Arch exp. Path. Pharmak.* **175**, 744.
5. Bock, C, and Hoffman, F. A. (1874) *Experimentalstudien uber Diabetes.* Berlin.
6 Boehm, R (1920). *Handbuch der Experimentellen Pharmakologie.* Berlin.
7. Burn, J. H (1946). *The Background of Therapeutics.* p. 242. Oxford University Press, London
8. Colasanti, G (1878). *Pfluq Arch. ges Physiol.* **16**, 157.
9 Cole, F (1946). *Anesthesiology.* **7**, 190.
10. Cole, F., Baronfsky, I. D, and Wangensteen, O. H. (1947). *Surgery,* **21**, 881.
11. Collier, H. O., Paris, S. K, and Woolf, L I. (1948) *Nature,* **161**, 817.
12. Cullen, S C (1944) *Anesthesiology* **5**, 166
13. Cushny, A. R (1928). *A Text-book of Pharmacology and Therapeutics,* p 316. J & A. Churchill, London.
14 Dale, H. H., and Laidlaw, P. P. (1911). *J Physiol* **41**, 1.
15. Dawkins, C J. M. (1947) *Brit. Med. J* **i**, 3.
16. Dixon, W. E., and Brodie, T G (1903) *J Physiol* **29**, 97.
17 Dock, F. W. (1872) *Pflug Arch ges Physiol.* **5**, 581.

18 Dobozy, E. (1940). *Orv. Hetil.* **84,** 25.
19 Edwards, P. M (1948). *Anæsthesia.* **4,** 160
20 Everett, G M. (1948). *J. Pharmacol.* **92,** 326.
21. Featherstone, R. M , and Gross, E. C. (1947). *Amer. J. Physiol* **148,** 507.
22. Feitelberg, S., and Pick, E. P. (1942) *Proc. Soc. exp. Biol. N.Y.* **49,** 654.
23. Gaskall, W. H. (1878-79) *J. Physiol.* **1,** 162.
24. Gayet, R , and Guillaume, M. (1934). *Ann Physiol. Physiochem biol* **10,** 532
25 Geiger, E (1931) *Arch. exp Path. Pharmak* **161,** 88.
26 Goetzner, P (1920). *Handbuch der Experimentellen Pharmakologie,* p 210 Julius Springer, Berlin.
27. Gray, T C., and Halton, J (1948) *Brit med. J.* **1,** 784.
27A Griffith, H R (1945) *J. Amer. med. Ass.* 127, 642.
28. Harroun, P , Becket, F. E , and Fisher, C. W. (1947). *Surg Gynec Obstet* 84, 491.
29. Harvey, A M., and Lilienthal, J. L. (1941). *Johns Hopk. Hosp. Bull.* **69,** 566
30. King, H (1935) *J. chem. Soc.* 1381.
(1935). *Nature* 135, 469.
31. Kellgren, J. H , McGowan, A J., and Wood, R D (1946). *Brit. med J.* **2,** 898.
32 Landmesser, C. M (1947) *Anesthesiology.* **8,** 506.
33. Langendroff, O (1887). *Arch. Anat. Physiol Suppl.* p 269
34. Leulier, A., and Vamhemis, G. (1935) *C. R Soc. Biol. Paris.* **118,** 256.
35 Macintosh, F C., and Paton, W. D. H. (1949) *J. Physiol.* **109,** 190.
36. McIntyre, A. R. (1947). *Curare* p 59, 158 University of Chicago Press, Chicago.
37 McIntyre, A R , and King, R E (1944) *Fed. Proc* **3,**
38 Pavlow, J (1878) *Pflug. Arch ges Physiol.* **16,** 272.
39 Pearlstein, M. A , and Weinglass, A (1944). *Amer. J. Dis Child.* **67,** 360.
40 Pick, E P., and Unna, K. (1945) *J. Pharmacol.* **83,** 59.
41 Poulssons (1938) *Pharmacology and Therapeutics.* p. 66. Heinemann, London
42. Prescott, F , Organe, G., and Rowbotham, S (1946). *Lancet.* **ii,** 80
43 Ruskin, A , Ewalt, J , and Dechard, G (1943) *Dis. Nerv. System,* **4,** 335
44 Schild, H O , and Gregory, R A *Proc XVII. Int. Physiol. Congress* p 288
45. Smith, S M Quote from McIntyre, A R *Curare* p. 179 University of Chicago Press, Chicago
46 Stern, L , and Rothlin, E. (1918) *Arch Sci. phys nat* Suppl 11-19. 4, 45
47 Sollman, T (1926) *A Manual of Pharmacology.* 6th ed p 421. W. B Saunders Co , Phil
48. Von Euler, V S , and Wahland, H (1941) *Acta physiol scand.* **2,** 327
49 Voison, A , and Lionville, H (1920) *Handbuch der Experimentellen Pharmakologie* p 187 Berlin
50 West, R (1938) *J Physiol* **91,** 437 (1938) *Lancet* **i,** 431
51. Whitacre, R J , and Fisher, H J (1945) *Anesthesiology.* **6,** 124
52. Wintersteiner, O , and Dutcher, J D (1943) *Science* **97,** 467

CHAPTER XXIII

SPECULATIONS CONCERNING CHOLINERGIC TRANSMISSION

THE dominant influence of the release and accumulation of acetylcholine (ACh) at the neuromuscular junction of skeletal muscles upon the intensity and the duration of action of d-tubocurarine chloride suggests that this same factor may play an even greater part than has heretofore been suggested in the sequence of loss of muscle tone in skeletal muscles occuring during blood-borne anæsthesia. It seems significant that, during blood-borne anæsthesia, in subjects with myasthenia gravis, and during curarisation, skeletal muscles lose their tone in the same order, viz. first in the extrinsic muscles of the eyes and small muscle groups, then in large muscle groups, next in the intercostal muscles and the sterno-costal fibres of the diaphragm, and finally in the crural fibres of the diaphragm.

During blood-borne anæsthesia, this sequence has been attributed to the order in which the motor cells of the central nervous system are depressed and so arrest the passage of nerve impulses to peripheral motor nerve endings, and, in turn, the release of ACh at the neuromuscular junction of specific groups of skeletal muscles. In myasthenia gravis, and during curarisation in conscious or lightly anæsthetised subjects, nerve impulses pass in a normal manner to peripheral motor nerve endings, but in each instance, ACh fails to attain fixation in skeletal muscle cells and striated muscles lose their tone.

Harvey and Lilienthal (1941) have emphasised the similarity between myasthenia gravis and curarisation. Thus, the sequence of loss of muscle tone in skeletal muscles is the same in both conditions. In both, muscle effectors such as potassium, guanidine, and adrenaline, and anticholinestrases such as eserine and prostigmine, produce a return of muscle tone, while—again in both conditions—quinine and procaine aggravate the atonic condition of skeletal muscle. In each instance, too, depression of muscle potential is

produced by a single maximal motor nerve stimulus. A further depression is produced by the second of a pair of maximal motor nerve volleys, and a series of motor nerve volleys results in the progressive diminution of the muscle action potential in both conditions. These observers state that the persistence of the transmitter and prolongation of end-plate potential may be the same process described in different terms. The absence of the transmitter, or depression of end-plate potential to a sufficient degree, produces loss of muscle tone in skeletal muscles; and it is known that electrical stimulation effects the release and eventual exhaustion of the combined acetylcholine content of skeletal muscles.

In myasthenia gravis, it has been concluded that the synthesis of combined ACh by skeletal muscle cells is deficient, and that loss of muscle tone occurs when the store of combined ACh in individual skeletal muscles is exhausted, for faulty synthesis prevents its sufficiently rapid replacement. The sequence of loss of muscle tone in subjects with myasthenia gravis might, therefore, be taken as a measure of the ability of individual muscles to synthesize ACh, and it might be assumed that the synthesis of combined ACh by skeletal muscles varied from group to group, being least in the extrinsic muscles of the eyes and small muscle groups, and greatest in the crural fibres of the diaphragm.

There is little doubt that tissue cells differ in their individual capacity to synthesize and store combined ACh. Thus, Chang and Gaddam (1933), Beznak (1934) and Loewi (1935) concluded that frog's heart contained many times the amount of ACh required to produce cardiac inhibition; Feldberg and Vartianan (1934) calculated that the superior cervical ganglion contained a store of ACh equivalent to the amount released by 2,000 stimuli. The ACh content of various parts of the central nervous system has been studied by many observers. It is found that the ability of various types of nervous tissue to synthesize ACh diminishes with phylogenetic development, and that the rate of its synthesis in dogs diminishes in the order: cerebral cortex, brain stem, medulla, spinal cord and cerebellar cortex; the hypothalamus has a relatively large capacity to synthesize ACh. Feldberg (1945) states that the ability to synthesize ACh does not run in parallel with the cholinesterase content of a given type of nervous tissue; while there is a close relationship in some types of nervous tissue,

in others the cholinesterase content bears no relationship to the ability to synthesize ACh. But in each species and at each age the balance of the synthesis, release and hydrolysis of ACh allows each individual type of nervous tissue to attain and maintain a certain definite and characteristic level of ACh, and each type of nervous tissue appears to be unable to build up a store of ACh greater than its normal physiological complement.

It is generally supposed that ACh is released from peripheral motor nerve endings to the neuromuscular junction of skeletal muscles; Feldberg (1945) states that muscle fibres contain no cholinesterase and little ACh. There is little reason to doubt that cholinesterase is concentrated at the site of its action, at the neuromuscular junction of skeletal muscles, and not in the muscle cells. Clark (1937) stated that all cells upon which ACh produced an action, themselves contain considerable stores of this substance, but it would probably be more correct to say that they contain a characteristic store of combined ACh, and synthesize combined ACh at a characteristic rate. Evidence has been discussed which suggests that combined ACh is synthesized within skeletal muscle cells to be released from thence to the neuromuscular junction; Mann *et al* (1938) observed *in vitro* that rat's diaphragm possessed about one-third of the ability of rat's brain to synthesize ACh. The ability of individual skeletal muscles to synthesize ACh has not yet been determined; but, if a parallel can be drawn with the central nervous system, it may be supposed that skeletal muscles differ in their individual ability to synthesize combined ACh. And the order of the loss of muscle tone in myasthenia gravis indicates that the ability to synthesize and store combined ACh is least in the intrinsic muscles of the eyes and small muscle groups, and increases progressively in large muscle groups, in the intercostal muscles and the sternocostal fibres of the diaphragm, to be greatest in the crural fibres of the diaphragm.

Loss of muscle tone during curarisation is an *adsorption* displacement mechanism, and the displacement of ACh from its specific receptors at the neuromuscular junction of skeletal muscles occurs—and the muscle loses its tone—when the concentration of d-tubo-curarine chloride reaches a certain critical concentration at the neuromuscular junction of the muscle. In Man, it is possible with divided doses of d-tubo-curarine chloride to depress muscle

tone selectively in particular groups of skeletal muscles. Thus, in a conscious subject the intravenous injection of 4 mgs. of d-tubo-curarine chloride renders only the extrinsic muscles of the eyes and the eyelids toneless. As the intravenous dose of d-tubo-curarine chloride is increased step by step, there is loss of muscle tone subsequently in small muscle groups, then in large muscle groups, in the intercostal muscles and sternocostal fibres of the diaphragm; finally, when the intravenous dose has reached about 30 mgs. all skeletal muscle becomes toneless. The pattern of this behaviour indicates that the quantum of ACh normally present at the neuro-muscular junction of skeletal muscles varies from muscle group to muscle group, being least in the extrinsic muscles of the eyes and greatest in the crural fibres of the diaphragm.

The return of muscle tone after full curarisation in conscious subjects indicates the time taken to achieve an effective concentration of ACh at the neuromuscular junction of skeletal muscles and, in turn, the rate of synthesis of combined ACh by individual muscle groups. In such a subject, muscle tone first returns in the crural fibres of the diaphragm, and it can be inferred that combined ACh is synthesized most rapidly in this skeletal muscle. Muscle tone then returns in the sternocostal fibres of the diaphragm and the intercostal muscles, next in large muscle groups, then in small muscle groups, and finally in the extrinsic muscles of the eyes; it can be concluded that this rate of recovery represents the rate of synthesis of combined ACh in these several groups of skeletal muscles. Hence, it appears that the quanta of ACh normally present at the neuromuscular junction of skeletal muscle in normal and myasthenic subjects varies in the same order as the ability of these several groups of skeletal muscles to synthesize ACh.

Loss of muscle tone in myasthenia gravis and during curarisation can, therefore, be attributed to the absence of an effective concentration of ACh at the neuromuscular junction of skeletal muscles. In each instance, the sequence of loss of muscle tone in skeletal muscles can be attributed to differences which exist in the rate of synthesis of combined ACh and the quanta of ACh normally present at the neuromuscular junction of particular groups of skeletal muscles. The extrinsic muscles of the eyes, which synthesize ACh most slowly and have the smallest normal quantum of ACh at their neuromuscular junction, are first to lose their tone.

And as these two factors progressively increase in value, small muscle groups, then large muscle groups, next intercostal muscles and the sternocostal fibres of the diaphragm, which synthesize ACh most rapidly and have the largest normal quantum of ACh at their neuromuscular junctions, are the last skeletal muscles to lose their tone in subjects with myasthenia gravis and during curarisation.

If this thesis is accepted, it follows that the curare-like action of anæsthetics must be assigned a more important rôle in the production of the sequence of loss of muscle tone in skeletal muscles which occurs during blood-borne anæsthesia; for, as the quantum of ACh is reduced at the neuromuscular junction in keeping with the arrest of effector impulses which reach this site, the curare-like action of blood-borne anæsthetics becomes effective, first in the extrinsic muscles of the eyes and small muscle groups whose normal quanta of ACh is the smallest, and whose rate of synthesis of ACh is slowest, and then in order: in large muscle groups, then the intercostal muscles and the sternocostal fibres of the diaphragm, and finally in the crural fibres of the diaphragm.

The evidence of the chemical transmitter at the neuromuscular junction of skeletal muscles raises the possibility of a chemical transmitter at synapses in the central nervous system. The action of ACh on autonomic ganglia or on motor end-plates initiates a wave of excitation in a nerve or in a muscle fibre; and the injection of sufficient ACh into an autonomic ganglion produces repetitive impulses in post-ganglionic fibres, while its injection into a skeletal muscle causes tetanic spasm of the muscle fibres. There is evidence that the stimulating effect of ACh on the neuromuscular junction or central synapse is produced by its depolarizing action at these sites, but in each instance, when ACh is applied artificially or accumulates in excess in the presence of eserine, the inability of the neuromuscular junction or central synapse to become polarised produces depression. Like ACh, eserine and prostigmine both produce a stimulant and a depressant action on the central nervous system. These central effects are sufficiently alike those of ACh to be explained by an accumulation of ACh produced by the anticholinesterase action of these substances. Moreover Bulbring and Burn (1941) showed that ACh produces an almost immediate action on the central nervous system, while with eserine and prostigmine there is a latent period followed by a

gradually increasing reaction as the anticholinesterase action of these substances permit ACh to accumulate. Thus, Miller (1937) applied eserine on blotting paper to the leg area of the motor cortex of cats and rabbits. Contraction of the muscles of the contralateral leg was produced, and followed by muscular rigidity of the limb. Tremor then developed within a few minutes, gradually giving way to clonus. These effects ceased a few minutes after the eserinized blotting paper was removed, and they were arrested promptly by the ablation of the eserinized area of the motor cortex. After eserine is injected intravenously, or when the intraventricular system is perfused with eserine solution, ACh increases in cerebrospinal fluid and its concentration in C.S.F. rises with the dose of eserine injected intravenously. Miller *et al* (1940) observed that the local application of ACh to the motor cortex of cats produced effects which resembled those of weak eserine, and if pronounced cortical activity is to be produced in the absence of an anticholinesterase, a strong concentration of ACh must be applied to the cortex. Brenner and Merritt (1942) state that ACh applied to the cortex in this fashion produced a localised effect which lasts for as long as ACh remains in contact with the cortex, and which resembles the electrical changes recorded in the human cortex during a convulsive seizure. Evidence has already been discussed which indicates that combined ACh is synthesized in the brain, and that various parts of the brain differ in the rate of its synthesis. Feldberg (1945) believes that tissue such as the brain, which exhibits continuous activity, is characterised by a low storage-capacity, but a relatively great ability to synthesize combined ACh. There is reason to believe that ACh is released, hydrolysed, and replaced at central synapses in the course of normal activity, but accumulates in excess of normal requirements in the presence of anticholinesterase. It is probable that any factor which effects the rapid release and/or the accumulation of ACh at central synapses may produce the stimulation of multitudes of central synapses, and the firing of a large number of central motor neurones, with the consequence of a general cerebral convulsion. If the probability of cholinergic transmission at central synapses is accepted as a working hypothesis, several interesting speculations may be made.

Mann *et al.* (1938) have shown *in vitro* that acid conditions,

heat, or narcotics in sufficient concentration, produce the rapid release of ACh from the cells of a rat's brain; and in clinical practice, the following effects are suggestive of excess of ACh at central synapses.

When severe asphyxia occurs during a short nitrous oxide anæsthetic for dental extractions, a generalised cerebral convulsion —termed a " jactitation "—may often occur. These jactitations may be attributed to the sudden general release of excess of ACh at the synapses of the central nervous system. They are invariably arrested when the airway is cleared, and excess of oxygen is administered by inhalation or insufflation.

Cortell *et al.* (1941) found no change in the ACh or the cholinesterase content of the brain of rabbits which had been subjected to a low oxygen partial pressure, and it is observed in clinical practice that jactitations do not occur when anoxia acts alone. Oxygen lack combined with the deficient excretion of carbon dioxide, however, not only produces jactitations, but also causes the appearance of ACh, or its increase, in the cerebrospinal fluid of eserinized dogs; this rise of ACh is independent of rise of arterial pressure and occurs after the suprarenal glands have been removed. McKail *et al* (1939) observed that carbon dioxide depressed the response of the cortex in a manner similar to excess of ACh, and found that the effect was readily abolished by atropine, and was sometimes potentiated by eserine. Feldberg (1945) considers that these results are strong presumptive evidence that carbon dioxide excess produces the excessive release of ACh; he believes that its action is mainly on the cortex, for spinal reflexes are relatively insensitive to carbon dioxide. Hence, jactitations during anæsthesia may be attributed to the generalized release of excess of ACh at central synapses, and their rapid cessation produced by excess of oxygen in the presence of a clear airway may be attributed to the rapid excretion of carbon dioxide and, in consequence, the arrest of the release of excess of ACh, and the rapid hydrolysis of accumulated ACh.

Since, *in vitro*, narcotics in a sufficient concentration produce the rapid release of ACh, the generalized convulsions which occasionally occur during deep blood-borne anæsthesia—the so-called ether convulsions—and those produced when a dangerously high concentration of a local anæsthetic is achieved in

circulating blood, may also be attributed to the excessive release and accumulation of ACh at central synapses produced in each instance by the presence of a high concentration of the narcotic in the cells of the brain. Generalized convulsions have been reported from time to time with all the anæsthetics in common clinical use: potent narcotics, such as the higher members of the methane series, whose physical properties permit them to be concentrated in the brain, are unsuitable for use in clinical anæsthetic practice because of their convulsant action. A factor common to all is the ability of narcotics in a sufficient concentration to hasten the release of ACh at central synapses. But during anæsthesia other occasional factors may also be present. Excess of carbon dioxide has already been discussed, and clinicians generally are convinced that hyperpyrexia is an occasional factor of importance. Mann *et al.* (1938) observed that heat hastened the release of ACh from the cells of the rat's brain, and Cortell *et al* (1941) found that fifteen minutes at 37° to 39° C., which produces coma in frogs, decreases the acetylcholine content and the cholinesterase activity of the central nervous system of these animals Clinically, hyperthermia may be an occasional factor in the production of convulsions during anæsthesia, but it is unlikely that it is a dominant factor In the Far East, for example, when room temperatures of 100° to 105° F. were experienced with a relative humidity of up to 87 per cent., body temperature during nitrous oxide-ether anæsthesia frequently rose to 103° to 105°F, but patients seldom if ever developed " ether convulsions "

Neither MacIntosh (1939), Mann *et al.* (1938), nor Cortell *et al* (1941) observed any alteration in the ACh content or the cholinesterase activity of the brain tissue of mice, rats, or rabbits during hypoglycæmic shock, Mann *et al* (1938) found that the ability of minced brain to synthesize ACh was the same in normal and insulin convulsed rats. Feldberg (1945) observed that glucose, in the concentration normally present in blood, inhibited the synthesis or the release of ACh. He suggested that blood glucose in normal concentration restrains the release of ACh to central synapses, and that hypoglycæmia produced by insulin removes the glucose " brake " and allows the release and subsequent accumulation of ACh at central synapses with, in consequence, a general convulsion. It will be realised too, that

the hyperglycæmia of clinical anæsthesia may inhibit the release of ACh at central synapses, so diminishing the release of ACh at the neuromuscular junction of skeletal muscles hastening the curare-like action of blood-borne anæsthetics at this site.

Minz (1936) observed that strong faradic stimulation of the isolated spinal cord of rabbits produced the release of ACh into the surrounding fluid medium. When the intraventricular system of dogs and cats was perfused with eserinized Locke solution, Adams *et al.* (1938) observed that stimulation of the motor cortex, the cerebellar cortex, or the spinal cord by a 50-cycle alternating current produced no increased output of ACh, but when a similar stimulus was applied to the hypothalamus, the acetylcholine content of the perfusate was approximately doubled in seven of the fourteen experiments. A constant current, however, produced no such effect.

During E.C.T., a 50-cycle alternating current of about 150 milliamps at about 150 volts is passed through the frontal region of the skull for a period of time which varies from 0·1 to 1·0 seconds. This results in violent muscular movement patterns, the onset of which may be instantaneous or may be delayed for as long as 60 to 90 seconds. The back is violently arched, the legs are extended, the lower jaw is powerfully elevated, the arms are adducted, the forearms are flexed and pronated, and the fingers are extended. This movement pattern is repeated from 3 to 5 times, becoming less violent with each successive repetition. This clonus may be attributed to excess of ACh at central synapses, or to the inefficient damping of the after-discharge, but it occurs even with the Strauss-MacPhail apparatus.[1]

During E.N.T., in contra-distinction, a 50-cycle alternating current at about 180 volts, gradually working up to a maximum of about 200 milliamps, is passed continuously through the frontal region of the skull for a time which varies from 6 to 20 minutes. And again a definite movement pattern is produced. In this instance, there is a generalized rigidity of the neck, back and legs; elevation of the lower jaw with retraction of the upper lip producing a typical snarl, the vocal cords are adducted—and the thorax fixed

[1] With the Strauss-MacPhail machine for E C T. a condensor is charged with a similar current The object of this machine is to produce a "square top" wave with the discharge of the condensor and damped oscillations in the after-discharge period

in the position of expiration; the arms are adducted at the shoulders and forearms are semiflexed and pronated, and the fingers are extended.

The observations of Adams *et al.* (1938) and the primitive movement pattern produced during E.C.T. and E.N.T., combine to suggest that electrical stimulation and/or the rise of pH. produced by it, result in the liberation of excess of ACh in the basal ganglia and particularly in the hypothalamus. During E.C.T. the sudden excessive release of ACh produced violent clonic movement patterns, which subside rapidly as the potent cholinesterase present at central synapses hydrolyses excess of ACh at this site. A delayed convulsion, when it occurs, can be attributed to the time taken to accumulate ACh at the central synapses in an effective convulsant concentration. During E.N.T. it can be assumed that the amount of ACh released at central synapses is insufficient to produce muscle clonus, but is sufficient to produce muscular rigidity for so long as the treatment is continued. It is observed during E.N.T., however, that muscular rigidity relaxes as treatment continues, and the current must therefore be increased progressively as treatment proceeds. At length, in a period of time which varies with the particular subject, even the maximum current fails to maintain rigidity: this might be attributed to the exhaustion of the combined ACh in the hypothalamus, combined with a rate of synthesis insufficient to permit continued accumulation of ACh at central synapses.

Harvey (1948) reported that prolonged treatment with di-isopropyl-fluorophosphonate (D.F.P.), which is a powerful anticholinesterase, produces an anxiety state. He observed, after daily intramuscular injections of D.F.P. of sufficient duration, that normal subjects developed insomnia, restlessness, excessive dreaming with nightmare, headaches, drowsiness, increased libido, mental confusion, visual hallucinations, and para-æsthesia. These effects were diminished by atropine but not by prostigmine or curarine. To date, the only known effect of D.F.P. is its ability to destroy cholinesterase. Harvey states that the production of this anxiety syndrome by a substance which has been shown to inhibit cholinesterase within the brain suggests that ACh plays a positive but as yet undefined rôle in central neural function. And the relief of psychiatric disorders by E.C.T. and E.N.T., which are presumed

to produce a brief sudden excess of ACh at central synapses in general and in the hypothalamus particularly, suggests that such disorders are related in some way with the synthesis and release of ACh at these sites in the central nervous system. Since fully curarised, lightly anæsthetised and adequately oxygenated subjects respond in a beneficial manner to E.C.T. and E.N.T., there is little doubt that neither muscle movement nor asphyxia are relevant factors; this suggests that the production and the relief of psychiatric disorders might well be linked with the mechanism of cholinergic transmission at the synapses of the central nervous system.

TABLE 48.

ACETYLCHOLINE FORMATION OF RAT'S BRAIN. (QUASTEL, 1950.)

1. Minced Rat Brain, eserinised in an Oxygen atmosphere at 37°C.		
Substrate	Acetylcholine formed, Y/g.	
Nil	2·8	
Sodium Lactate	9·5	
Sodium Pyruvate	11·4	
Sodium Succinate	2·8	
Glucose	11·1	
2. Rat Brain Slices, eserinised at 37°C.		
Substrate	Acetylcholine formed, Y/g.	
	Ærobic	Anærobic
Nil	3·5	1·5
Glucose	27·9	2·0

Finally, one must speculate on how the inhibition of the oxidation of glucose, lactate and pyruvate produces the state known as narcosis. Reference to Figure 15 indicates that the ærobic oxidation of these metabolites form an important link in the chain of events which results in the synthesis of combined ACh. Table 48 shows that under ærobic conditions, the oxidation of glucose, lactate and pyruvate gives rise to a product or a set of circumstances which enables combined ACh to be synthesized freely while under anærobic conditions the synthesis of ACh to all intent and purposes ceases. It is observed too, that although there is a definite uptake of oxygen by the brain tissue, no synthesis of combined ACh occurs in the presence of succinate. Hence, the synthesis of combined ACh cannot depend merely on the presence of oxygen or the uptake of oxygen by the brain tissue and this infers that its

synthesis depends either on the energy supplied by the oxidation of glucose, lactate and pyruvate or on the presence of a specific metabolite produced during the ærobic oxidation of these metabolites.

TABLE 49.

THE SYNTHESIS OF ACETYLCHOLINE BY BRAIN ACETONE POWDER IN THE PRESENCE OF ADENOSINO TRIPHOSPHATE (ANÆROBIC) (NACHMANSOHN AND MACHADO, 1943)

Adenosino Triphosphate present in mg.	Acetylcholine formed, Y/g.
0	6
0·01	7 5
0 05	113
0 1	155
0 2	212

It is known that a relatively large amount of energy rich adenosino-triphosphate (ATP) is formed during the ærobic oxidation of glucose, lactate and pyruvate, and Nachmansohn and Machado (1943) have shown in Table 49 that the synthesis of ACh by brain acetone powder varies as the amount of ATP present. Harpur and Quastel (1949) found moreover that the rate of ACh synthesis by intact brain tissues depends not only on the rate of ATP formation but also on the presence of the cozymase, di-phospho-pyridine nucleotide (DPN).

Under ærobic conditions, it has been seen that narcotics inhibit the synthesis of combined ACh. This result is consistent with the decreased oxidation of glucose, lactate and pyruvate produced by narcotics, for the inhibition of the oxidation of these metabolites *results in a diminution in the rate of formation of ATP.* Eiler and McEwen (1949) have shown that pentobarbital inhibits the production of high-energy phosphate bonds with brain tissue in keeping with its ability to reduce the utilization of oxygen by this tissue and they observed that pentobarbital reduces the oxidation of pyruvate and the uptake of phosphate by brain tissue in like proportion. Hence there is strong presumptive evidence that narcotics inhibit the synthesis of combined ACh by depressing the rate of formation of energy rich ATP by brain cells and that this results in the inability of these cells to maintain their normal

functional activity. Eiler and McEwen (1949) claim that succinate oxidation which is uninfluenced by narcotics, can effect the synthesis of ATP and it is presumed, the formation of ACh. If this was in fact so, it would explain the saving action of succinate metabolism during narcosis.

References.

1. Adams, H. M., McKail, R. A., Obrador, S., and Wilson, W. C. (1938). *Jour. Physiol.* 93, 45P.
2. Beznak, A. B. L. (1934). *Jour. Physiol.* 82, 129.
3. Brenner, C., and Merritt, H. H. (1942). *Arch. Neur. & Psychiat.* 48, 382.
4. Bulbring, E., and Burn, J. H. (1941) *Jour. Physiol.* 100, 337.
5. Chang, H. C., and Gaddam, J. H. (1933). *Jour. Physiol.* 79, 225.
6. Clark, A. J. (1937). *Handbuch der Experimentellen Pharmakologie.* Berlin. p 71.
7. Cortell, R., Feldman, J, and Gellhorn, G. (1941). *Am. Jour. Physiol.* 132, 588.
8. Eiler, J. J., and McEwen, W. K. (1949). *Arch Biochem.* 20, 163.
9. Feldberg, W. (1945). *Physiol. Rev.* 25, No. 4, 496.
10. Feldberg, W., and Vartianian, A. (1934). *Jour. Physiol.* 83, 103.
11. Harpur, R. P., and Quastel, J. H. (1949). "Nature." 164, 779.
12. Harvey, A. M. (1948). *Bull. John Hopkins Hosp.* 83, No. 6, 600.
13. Harvey, A. M., and Lilienthal, J. L, Jun. (1941). *Bull. John Hopkins Hosp.* 69, 566.
14. Loewe, O. (1938). *Proc. Roy. Soc.* B118, 299.
15. MacIntosh, F. C. (1939). *Jour. Physiol.* 96, 6P.
16. McKail, R. A., Obrador, S, and Wilson, W. C. (1939) *Jour. Physiol.* 99, 312.
17. Mann, P J G, Tennenbaum, M, and Quastel, J. H. (1938). *Biochem. Jour* 32, 243
18. Miller, F R. (1937) *Jour. Physiol* 91, 212.
19. Miller, F R, Stavraky, G. W., and Woonton, G. A. (1940). *Jour. Neurophysiol.* 3, 131.
20. Minz, B. (1936) *Comp. Rend. soc. biol Paris.* 122, 1214
21. Nachmanson, D, and Machado, A L. (1943) *J. Neurophysiol.* 6, 397.
22. Quastel, J. H (1950). International Conference on Narcosis, Paris. Personal communication

PART FOUR

METABOLISM DURING ANAESTHESIA

CHAPTER XXIV

INTRODUCTION

THE physical properties of many narcotics are such that they cannot be concentrated in an effective concentration at the site of anæsthetic drug fixation in the cells of a heterogeneous cell system such as Man. Such narcotics are, therefore, inert when used as anæsthetics. Moreover, many narcotics, whose physical properties do permit them to be concentrated in an effective concentration at the site of anæsthetic drug fixation in Man, must be excluded from clinical anæsthetic practice because of harmful side-actions.

During the past hundred years, anæsthetics with deleterious side-actions have been distinguished and discarded from clinical anæsthetic practice, and this process of clinical selection continues to be exercised. The anæsthetics to be discussed consist of those which have to date survived this process of selection and whose side-actions are not sufficiently harmful to warrant their exclusion from clinical practice. It is proposed to discuss the metabolic and physiological disturbances which they produce during clinical anæsthesia, firstly in terms of their dominant pharmacological action, and secondly in terms of the deleterious side-actions which particular members possess.

On the basis of the observations of Quastel and Wheatley (1932), it has been concluded that narcotics restrict the carbohydrate metabolism of living cells solely to that produced by the oxidation of succinic acid, which, it is assumed, provides the minimum amount of carbohydrate energy compatible with the continued life of the cell. Because of the specificity of the depression of carbohydrate metabolism by narcotics, and the "saving action" of succinate metabolism, these observers conclude that narcotics cannot be considered tissue poisons and in unicellular organisms leading an independent existence, there is every reason to accept this view.

In like manner, the anæsthetics in common clinical use do not act as tissue poisons on the cells of a heterogeneous cell system

such as Man, and the standard sequence of depression of the body by inhalation anæsthetics, such as ether, affords ample evidence of this fact.

TABLE 50.

THE ETHER CONCENTRATION OF THE INTERNAL JUGULAR VEIN

(Grams per litre) (Modified from Haggard)

Level of Anæsthetic Depression	Experiment 1	Experiment 2	Experiment 3	Average
Anæsthetic sleep	0 43	0 39	0·46	0 42
Corneal reflex absent	1·19	1 21	1·17	1 19
Muscular relaxation	1·36	1 35	—	1·36
Respiratory failure	1·61	1·70	1 54	1·62

The concentration of ether in the venous blood of the internal jugular vein during anæsthesia may be used as a measure of the average ether content of the brain. Table 50, taken from the observations of Haggard (1924), shows that consciousness is lost when the ether content of venous blood of the internal jugular vein has reached a concentration of about 0 42 grams of ether per litre. A concentration of ether in the brain equivalent to 0 42 grams per litre in the blood of the internal jugular vein is, therefore, an effective concentration for the cells of the higher centres of the brain. When the concentration of ether in the blood of the internal jugular vein has reached about 1·19 grams per litre, the ability to react in a reflex manner to external stimulus is lost, and it can be assumed that the equivalent concentration in the brain is an effective concentration for the areas of sensory co-ordination of the brain At this point, however, the concentration of ether in the higher centres of the brain is more than twice that required to produce anæsthetic depression of the cells of the higher centres, but these cells are not injured by this " greater than anæsthetic concentration," and recover completely when the anæsthetic is withdrawn When the concentration of ether in the brain reaches a concentration equivalent to 1·36 grams per litre in the blood of the internal jugular vein, it is an effective concentration for the areas of motor co-ordination of the brain, for muscle tone is abolished in all striated muscles except the

diaphragm. This concentration, which is more than three times greater than the concentration required to produce anæsthetic depression of the cells of the higher centres, is 115 per cent. of the effective anæsthetic concentration of ether required to depress the areas of sensory co-ordination of the brain; these cells, however, suffer no damage, and recover completely when the anæsthetic is withdrawn. The concentration of ether in the brain becomes an effective concentration for the cells of the respiratory centre and breathing ceases when the venous blood of the internal jugular vein contains 1·62 grams of ether per litre. Reference to Table 50 shows that this is almost four times greater than the concentration required to depress the cells of the higher centres, it is 136 per cent. of the minimum effective anæsthetic concentration required to depress the areas of sensory co-ordination, and is 119 per cent. of the minimum effective concentration required to depress the cells of the areas of motor co-ordination of the brain. In these circumstances, if the excretion of carbon dioxide and the uptake of oxygen is maintained within normal physiological limits by effective artificial respiration with an oxygen atmosphere, neither loss of consciousness, loss of the ability to react to external stimulus, nor loss of muscle tone becomes more intense by virtue of the " greater than anæsthetic concentration " in these centres of functional activity, and moreover, the cells of these centres suffer no damage and recover completely when the anæsthetic is withdrawn.

The conception of the fixation of anæsthetics by specific receptors located in the cell surface offers an explanation of this phenomenon.

The probable nature of anæsthetic receptors suggests that each specific area of functional activity of the brain possesses a characteristic number of receptors which will fix anæsthetics, and when all the available anæsthetic receptors of a given type of cell have been occupied by an anæsthetic, drug fixation has reached its maximum value; consequently, anæsthetic depression reaches its greatest intensity. When maximum drug fixation has been attained, a further increase in the concentration of the anæsthetic in extracellular fluid can produce no further anæsthetic action, but will result in a corresponding increase in the concentration of the anæsthetic in solution in the cell itself.

The observations of Hiller (1927) and Marsland (1934) indicate that unfixed narcotic in solution in the cell substance does not produce narcosis, but in sufficient concentration can react chemically with living protoplasm. It has been shown when a certain critical concentration of anæsthetic is dissolved in living cells that an irreversible precipitation of cell protoplasm occurs. Hence, an increase in the concentration of the anæsthetic above that required to produce maximum fixation cannot further intensify the degree of anæsthetic depression in living cells; and, in the absence of side-actions, it produces no further biological response of any kind, unless and until its concentration in solution in the cell reaches the critical precipitation concentration of the anæsthetic for that type of cell, when an irreversible precipitation of the cell protoplasm occurs.

It can be assumed in the example quoted that all the available anæsthetic receptors in the cells of the higher centres of the brain have been occupied when the concentration of ether in these cells is equivalent to 0·42 grams of ether per litre in the blood of the internal jugular vein. As the concentration of ether in the brain progressively increases to a value equivalent to 1·19, 1·36 and 1·62 grams of ether per litre in the blood of the internal jugular vein, the response of the subject indicates that maximum anæsthetic fixation has been successfully achieved in the areas of sensory co-ordination, the areas of motor co-ordination of the brain, and finally in the respiratory centre. In each instance, as the concentration of ether representing maximum fixation is exceeded, neither loss of consciousness, loss of the ability to react in a reflex manner to external stimulus, nor loss of muscle tone become more intense. Because the cells of the several areas of functional activity of the brain suffer no damage from a concentration of ether equivalent to 1·62 grams of ether per litre in the blood of the internal jugular vein, and because they recover completely when the anæsthetic is withdrawn, it is clear that this concentration of ether is below the critical concentration necessary to precipitate cell protoplasm in these several centres of functional activity

In a properly conducted anæsthetic, the concentration of the anæsthetic in non-nervous tissues is always below the minimum threshold concentration necessary to produce anæsthetic depression

in these cells, and is always below the critical precipitation concentration for all types of cell protoplasm. When an anæsthetic without deleterious side-actions is used in clinical practice in a proper manner, it can, therefore, be concluded that the anæsthetic *does not act as a tissue poison* on the cells of a heterogeneous cell system such as Man.

Although the specific action of the anæsthetics in common clinical use does nothing to injure or poison the individual tissue cells on which they act, a definite syndrome of metabolic and physiological disturbance follows their use in clinical anæsthetic practice. In a heterogeneous cell system such as Man, the " division of labour "—produced by the specialisation of groups of cells during evolutionary development—has rendered the well-being of the whole body dependent upon the individual efficiency of its contained and interdependent organs. In consequence of this, the abolition of the functional activity of the great adjustor mechanism, the brain, wholly or in part, can be expected to modify the functional activity of individual organs and systems, and, in turn, that of the body itself.

When the functional activity of the brain is depressed by anæsthetics, the metabolic and physiological activity of the body is modified in keeping with the level of depression of this organ, and the specific inhibition of the carbohydrate metabolism which produces this state of anæsthetic depression in brain cells can also be expected to modify the metabolic activity of the body. These two factors combine to determine the character and the intensity of the upset produced by the dominant action of anæsthetics in Man. It is proposed to discuss the metabolic and physiological disturbances associated with dominant action of anæsthetics in Man, and then the dominant and side-action of anæsthetics on individual organs and systems.

References

1 Haggard, H W. (1924) *J Biol Chem.* 59, 771
2. Hiller, S. (1927) *Proc. Soc Exp. Biol N Y* 24, 427, 938
3 Marsland, D. (1934) *J Cell. Comp Physiol* 4, 9
4 Quastel, J. H , and Wheatley, A. H M (1932) *Biochem J.* 26, 725, 1672.

CHAPTER XXV

THE METABOLIC AND PHYSIOLOGICAL DISTURBANCES ATTRIBUTED TO THE DOMINANT PHARMACOLOGICAL ACTION OF ANÆSTHETICS

IT has been concluded, when the standard sequence of anæsthetic depression obtains, that the higher centres of the brain are depressed first, and the clinical signs appearing at this level of anæsthetic depression coincide so closely with those observed during light natural sleep that, in this discussion, this level of anæsthesia has been termed "anæsthetic sleep" Although the mechanism of the production of natural diurnal sleep differs from that of anæsthetic sleep and has still to be solved, it is difficult to escape the suggestion that the functional activity of the brain is in each instance depressed to the same level. In each instance, loss of consciousness, flaccid muscles reacting to external stimulus, and small pupils reacting to light indicate depression of the higher centres and a raised threshold of the areas of sensory co-ordination to external stimulus.

In deep natural sleep which, according to Kleitman (1929) and others, seldom lasts for more than about thirty minutes, relaxed muscles, the absence of knee jerks and of deep reflexes, and the presence of an extensor Babinski reflex indicate considerable depression of the areas of sensory and motor co-ordination of the brain; but the body muscles still react to intensely painful stimuli, and deep natural sleep is comparable with the level of anæsthesia just prior to the complete depression of the areas of sensory co-ordination of the brain The analogy, however, goes no further, for sleep comparable with anæsthesia to the level of the complete depression of the areas of motor co-ordination, or to the level of depression of the respiratory centre, has a pathological basis and is termed *coma*

Depression of the central nervous system which occurs during natural sleep is characterised by a diminution of the metabolic rate

of the body, by a disturbed water balance with water retention, and by a tendency to acidæmia. The modifications of the normal resting metabolism during natural sleep are discussed in detail below, for they provide a standard with which to compare the metabolic upset associated with anæsthesia of a corresponding level of depression.

Benedict (1915) and others have shown that the metabolic rate of the body may be reduced as much as 13 - 20 per cent. below the normal resting level during natural sleep. The body temperature may fall from one to two degrees centigrade, and Aron (1923) observed a 60 per cent. decrease of heat production in a boy of six years, and a 75 per cent. decrease in that of a girl of fifteen years during natural sleep. Boas (1932-33) and others observed decrease in pulse rate, and Hopkins (1935) noted a diminution of cardiac output during natural sleep. When this is coupled with the arteriolar vasodilatation reported by Kleitman, a fall of blood pressure must be anticipated. Hill (1898), Shepard (1914), and others have shown that the systolic blood pressure falls during natural sleep in parallel with the decrease in pulse rate; and Landis (1925-27) concluded that the fall of blood pressure was proportional to the depth of natural sleep. Kleitman (1929) observed a decrease in depth, an increase in the rate, and a prolongation of the expiratory phase, of respiration during sleep. In light sleep, the rhythm of respiration may be irregular; in deep sleep the most characteristic features are the regularity of respiratory rhythm and the diminution of the volume of lung ventilation. The oxygen consumption is decreased and the carbon dioxide tension of alveolar air is increased during natural sleep Grollman (1930) concludes that the decrease of oxygen consumption, body temperature, pulse rate, cardiac output, blood pressure, and the arteriovenous oxygen difference below the resting level indicate that metabolism is diminished below the resting level during natural sleep.

Ebbecke (1926) states that all the secretions of the body are diminished during natural sleep and that there is a retention of water by the body with a compensatory increased excretion of water on awakening. Thus, in normal conditions of life, the daily secretion of urine in a temperate climate is 1,500 cubic centimetres, of which 500 cubic centimetres are secreted during sleep and 1000 cubic centimetres during the waking hours. Consequently, there is

a nitrogen retention during sleep with a compensatory increased secretion of non-protein nitrogen on awakening. Lacrimal, salivary and glandular secretions generally are diminished during natural sleep. The lowered metabolic rate, with consequent diminution of the minute blood flow through individual organs, is responsible in part for diminished secretions, but the raised threshold to stimulus during natural sleep is also a factor of considerable importance.

There is an increase in the plasma volume of circulating blood during natural sleep, and Gollwitzer-Meier and Kroetz (1924) concluded that this is due to a definite water shift, for tissue fluids poor in protein and rich in sodium chloride and phosphates diffuse during natural sleep from the tissue spaces to the vascular system. The blood therefore is diluted, blood proteins, serum globulin and serum albumin are reduced in value, the specific gravity of blood falls, and hæmo-dilution occurs with a reduction in the number of erythrocytes and the hæmoglobin percentage. Blood cholesterol falls, but blood sodium, blood chlorides and blood phosphates increase in value. Kleitman (1929) states that the bicarbonate, potassium and calcium content of blood is unaltered during natural sleep Consistent results have not been observed in respect to blood calcium, but Cooperman (1936) concluded that the total serum calcium decreased during natural sleep and that this result could be correlated with the increase in plasma volume. Hopkins (1935-36) demonstrated that as the calcium content of blood decreased during sleep, so the inorganic phosphate content of the blood increased, and that the extent of this shift was greater in epileptics than in normal subjects.

Collip (1920) and Kunze (1928) have both reported a slight rise in the hydrogen ion concentration of the blood during natural sleep, but the alkali reserve has generally been found normal or slightly diminished. Diminished blood sodium and increased blood phosphates suggest a diminution of the alkali reserve during natural sleep, and the increased tension of carbon dioxide in alveolar air and arterial blood—together with the secretion of highly acid urine, rich in phosphates and ammonia—strengthens the view that a compensated acidæmia of a minor degree occurs during natural sleep

In section (1) of Table 51, the various factors which are

TABLE 51.

	Metabolic and Physiological Disturbances in	Natural Sleep	Anæsthetic Sleep
	Metabolic rate	Decreased	Decreased
	Body temperature	Decreased	Decreased
	Heat production	Decreased	Decreased
	Pulse rate	Decreased	±
	Cardiac output	Decreased	Decreased
	Vasodilatation	Increased	Increased
	Blood pressure	Decreased	Decreased
	Depth of Respiration	Decreased	Decreased
	Respiratory rate	Increased	Increased
	Respiratory volume	Decreased	Decreased
	Oxygen utilisation	Decreased	Decreased
	Alveolar carbon dioxide	Increased	Increased
	Arterial carbon dioxide	Increased	Increased
	Arterio-venous oxygen difference	Decreased	
Section 1	Body secretions	Diminished	Diminished
	Body fluids	Retention	Retention
	Urinary secretion	Diminished	Diminished
	Total N P.N. excretion	Diminished	Diminished
	Lacrimal secretion	Diminished	Diminished
	Glandular secretion	Diminished	Diminished
	Plasma volume	Increased	±
	Blood specific gravity	Diminished	±
	Blood protein	Decreased	±
	Serum globulin	Decreased	±
	Serum albumin	Decreased	±
	Erythrocytes	Decreased	±
	Hæmoglobin per cent	Decreased	±
	Blood Cholesterol	Decreased	Increased
	Blood sodium	Increased	
	Blood chlorides	Increased	Increased
	Blood phosphates	Increased	Increased
	Plasma bicarbonate	Tends to fall	Diminished
	Blood potassium	Unaltered	Decreased
	Blood calcium	Decreased	Decreased
	pH of blood	Tends to rise	Tends to rise
	Alkali reserve	Tends to fall	Diminished
	Urinary reaction	Acid	Acid
	Brain volume	Increased	Increased
	Intracranial pressure	Increased	Increased
Section 2	Blood glucose		Increased
	Blood lactic acid		Increased

modified during natural sleep are set out, in the order in which they have been discussed above, together with the reactions of these same factors in an *adequately premedicated subject during* blood-borne anæsthesia Except blood cholesterol, which is increased during anæsthesia, the factors tabulated are seen to be modified in the same direction during blood-borne anæsthesia as during natural sleep. In the case of plasma volume, and the factors which can be influenced by it, a $\pm$ sign is shown for the reaction of these factors during anæsthesia, because it has been reported that plasma volume during anæsthesia varies with the anæsthetic drug employed.

The changes in the metabolic and physiological activity of the body occurring during natural sleep have, therefore, much in common with those observed in an adequately premedicated subject during anæsthetic depression to a level just short of complete sensory loss. Light natural sleep corresponds closely with anæsthesia to the level of depression of the higher centres of the brain, and deep natural sleep to that of anæsthesia to a level just short of the depression of the areas of sensory co-ordination of the brain.

In an un-premedicated subject, the picture of anæsthesia to the level of depression of the higher centres of the brain may be distorted in a fantastic manner by the results of excessive psychic upset, causing the metabolic and physiological disturbance to resemble anything other than natural sleep.

Subjects who are afraid to go to sleep, just don't, and in normal conditions of life the onset of natural sleep and awakening are rapid and free from emotion. The mental approach of a normal subject to an anæsthetic, however, is the very antithesis of this, and most subjects think of an anæsthetic with considerable *apprehension and dread. But although afraid of an anæsthetic* the subject yet submits; without premedication, the induction of anæsthetic sleep may be associated with considerable emotional stress, accentuated sometimes by restlessness or violent struggling The most significant result of emotional and physical stress during anæsthetic induction is the secretion of excessive amounts of adrenaline into circulating blood.

As a result, the metabolic rate is increased and body temperature rises with vasodilation and the secretion of sweat. Lung ventilation, oxygen consumption, and the excretion of carbon

dioxide is increased in keeping with the increased metabolic rate; the character of breathing may assume almost any imaginable type of rhythm, and overbreathing may produce an acapnia. The heart accelerates, the pulse quickens, and cardiac output is increased—partly by the increase in the heart rate, and partly by an increase in the stroke volume. The coronary vessels dilate and the peripheral capillaries are constricted, and, in consequence, the blood pressure rises and extrasystoles may occur. In response to the rise of blood pressure, the heart is slowed through the sinus and aortic nerves, and the peripheral arterioles dilate with consequent fall of blood pressure from its high level. When, in addition, external stimulus is permitted during the stage of non-cooperative stupor, the response may be exaggerated and excessive, for this is the period of diminished cortical control of the lower brain centres (in particular of the hypothalamus), and excessive vagal action may result in complete heart block or syncope. Excessive reaction to external stimulus also causes an increase in the secretion of the lacrimal, salivary and bronchial glands; but, because of the vasoconstriction of the renal arteries produced by excess of adrenaline, the secretion of the kidneys does not always increase with rise of blood pressure. The powerful contraction of the spleen produced by excess of adrenaline causes an increase in the red-cell, white-cell and platelet count of circulating blood, and excess of adrenaline also stimulates the conversion of liver glycogen into glucose and muscle glycogen into lactic acid, with consequent rise in the glucose and lactic acid content of circulating blood.

As anæsthesia deepens and depression of the higher centres is followed by the depression of the areas of sensory co-ordination of the brain, emotional and physical stress ceases and the secretion of adrenaline falls; the metabolic rate and, in turn, the activity of the cardiovascular and respiratory systems diminish in keeping with the level of depression of the brain. The sweat, lacrimal, salivary, and bronchial glands cease to secrete, and urinary secretion is reduced to a low level. The glucose and lactic acid content of circulating blood falls, but does not return to its resting level.

In the absence of emotional and physical stress, however, the metabolic and physiological disturbances occurring during the anæsthetic depression of the body to the level of complete sensory

loss are similar to those observed during deep natural sleep. In modern anæsthetic practice, emotional and physical stress during this period can be abolished by the use of adequate premedication, the exclusion of external stimulation by efficient nursing, and rapid induction to the level of depression of the areas of sensory co-ordination of the brain.

Anæsthesia to the level of depression of the areas of motor co-ordination of the brain has no parallel in normal conditions of life; if this depth of anæsthesia is considered solely in terms of depression of the central nervous system to this level, then the resulting disturbance in the metabolic and physiological activity of the body consists of an intensification of all the factors affected during deep natural sleep, *plus* the results which follow complete loss of tone in the muscles of the extremities and the trunk.

The most significant result of anæsthesia to this level is a further diminution of the metabolic rate of the body, which, in the absence of other factors, causes a bradycardia, a diminished cardiac output, and a fall of blood pressure with vasoconstriction. On this account, too, breathing becomes shallow, its rate increases, the minute volume of lung ventilation falls, there is also reason to believe that the oxygen utilisation rate falls, and the carbon dioxide content of alveolar air and, in turn, that of arterial blood, increase. The body secretions fall in keeping with the lowered metabolic rate, and secretions such as tears, saliva, etc., which depend upon afferent impulses from without, cease. Table 53 shows that urinary secretion falls to a very low level and may to all intent and purpose cease. The only unimpaired form of fluid loss at this depth of anæsthesia is the secretion of water vapour in expired air, and there is an almost complete water retention. The diminution of the metabolic rate also leads to diminished heat production, and heat loss is now limited to the excretion of water vapour in expired air and to radiation, convection, and conduction. Because breathing is shallow, because vasoconstriction reduces the effectiveness of radiation, convection, and conduction and, most of all, because the subject is now almost poikilothermic, heat loss may be inadequate and the body temperature may rise by as much as 1°C

To the results which follow a reduction of the metabolic rate must be added those which follow loss of tone in the muscles of

the extremities and the trunk. In normal conditions of life, the return of venous blood to the right heart depends upon muscular movement, the support afforded to the veins by muscle tone, and the aspirating effect of the negative intrapleural pressure produced on inspiration. At this depth of anæsthesia the absence of muscle movement, the loss of muscle tone, and the diminished negative intrapleural pressure associated with shallow breathing all combine to hinder the return of venous blood to the right heart, and so cause a diminished cardiac output with, in turn, fall of blood pressure. The intensity of the embarrassment of the cardiovascular system produced in this fashion proves to be of little consequence in view of the lowered metabolic rate, providing it does not act for longer than about sixty minutes; if these factors continue to act for longer, signs of cardiovascular distress soon appear and the vicious circle of fall of blood pressure and anoxia rapidly produces cardiac failure. The diminished venous return may be effectively neutralised by the intravenous transfusion of whole blood

Considered solely in terms of the depression of the central nervous system, the disturbances of the metabolic and physiological activities of the body associated with anæsthesia to the level of complete depression of the areas of motor co-ordination of the brain consist of an intensification of the disturbances which have been seen to occur during deep natural sleep. There is greater diminution of the metabolic rate, with all that this implies, a greater tendency to acidæmia, a greater diminution of body secretions, cessation of urinary secretion and almost complete water retention. It must be added that if this depth of anæsthesia is maintained for too long, a diminished venous return which may readily bring about dangerous, if not fatal, cardiovascular distress.

If the level of depression of the brain was the only relevant factor acting during anæsthesia, the above disturbance of the metabolic and physiological activities of the body would represent a fairly complete picture of the modifications of the functional activity of the body to be expected during anæsthesia. In contradistinction to natural sleep, however, anæsthesia is produced by the inhibition of the oxidation of specific carbohydrate metabolites necessary to the normal autonomic activity of the cells of the brain. It is to be expected in a heterogeneous cell system such as

Man that this inhibition of the carbohydrate metabolism of the brain should be followed by a material and significant disturbance of the carbohydrate metabolism of the body taken as a whole. And the most striking, the most constant and one of the most consequential disturbances of metabolism during anæsthesia is the rise in the glucose and lactic acid content of circulating blood. Hyperglycæmia invariably occurs during all forms of anæsthesia. It has been observed during inhalation, rectal and intravenous anæsthesia, after the injection of hypnotics such as morphia or their ingestion orally, and in local anæsthetics when infiltration, regional and spinal nerve block are employed.

TABLE 52.

Duration of anæsthesia (minutes)	Blood sugar (milligrams per centum)				
	Case 1	Case 2	Case 3	Case 4	Case 5
− 60	90	—	—	—	—
0	106	78	80	82	84
10	185	108	127	102	95 *
18	144	—	—	—	—
45	—	—	—	—	95
60	—	—	—	—	—
90	155 *	152 *	134 *	124 *	—
120	—	—	79	110	—
180	—	75	77	88	—
210	—	80	—	—	—

* *Indicates the blood sugar at the greatest depth of anæsthesia obtained.*

In an unpremedicated subject, anæsthetic induction may be associated with considerable emotional and physical stress, causing the secretion of excess of adrenaline into circulating blood which, in turn, produces rapid glycogenolysis with a corresponding rise of blood sugar. The blood sugar values taken before and at the end of anæsthetic induction in Case 1 of Table 52 illustrate the glycogenolytic action of adrenaline produced by emotional and physical stress Case 1 was a nervous healthy soldier of 29 years, with a normal resting blood sugar of 86 milligrams per cent., who was to be operated on for an internal derangement of the knee at 9 a.m.

At 8 a.m. on the morning of operation, venepuncture was performed and a sample of blood was obtained containing 90 milligrams of sugar per cent. He was obviously upset by this procedure, but no explanation was offered for this break of normal routine. At 8.30 a.m., atropine (gr. 1/100) was injected subcutaneously. Again no attempt was made to allay his apprehen-

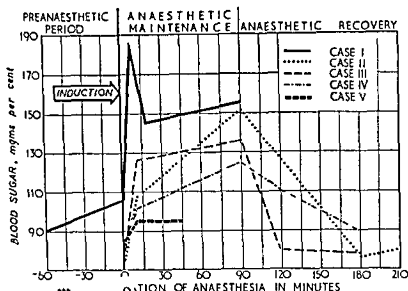


FIGURE 17.

sion, or protect him from external stimulation during this pre-anæsthetic period, and his blood sugar taken just prior to anæsthetic induction at 9 a.m. was 106 milligrams per cent. This increase of blood sugar during the pre-anæsthetic period to 23 per cent. above the normal resting level of this nervous subject, in whom emotional stress had been ignored and even aggravated, is in marked contrast to the normal blood sugar value of 78, 80, 82 and 84 milligrams per cent. in the corresponding blood samples of Cases 2-5, in whom pre-anæsthetic medication was adequate and pre-anæsthetic nursing was efficient. It can be concluded that a pre-anæsthetic rise of blood sugar may be caused by excess of adrenaline produced by emotional stress during this period, and that it can be effectively prevented by adequate premedication and efficient pre-anæsthetic nursing.

Returning to Case 1, the subject was then induced with too small a dose of cyclonal injected intravenously, and this was followed by nitrous oxide, oxygen and ether. Ten minutes later, at the end of a stormy induction in which anoxia was avoided, anæsthesia to the level of depression of the areas of sensory co-ordination of the brain had been achieved. A blood sample taken at the end of this period contained 185 milligrams of sugar per cent.—a rise of 115 per cent. above the subject's resting blood sugar value. In Cases 2-4, adequate premedication and efficient pre-anæsthetic nursing were followed by a swift and trouble-free induction with intravenous pentothal, nitrous oxide, oxygen and ether, to the level of depression of the areas of sensory co-ordination of the brain. Blood samples taken at the end of this period contained 108, 127 and 102 milligrams of sugar per cent respectively.

The excessive rise of blood sugar in Case 1, in whom emotional and physical stress was aggravated during anæsthetic induction, is in marked contrast to the moderate rise of blood sugar in Cases 2-4, in whom emotional and physical stress was relieved by adequate premedication, efficient pre-anæsthetic nursing, and a swift and trouble-free induction without anoxia. In Case 1, there is little doubt that excess of adrenaline produced by emotional and physical stress was the dominant factor responsible for the striking rise of blood sugar In Cases 2-4, the effective neutralisa[illegible] f emotional and physical stress throughout makes it doubtf[illegible] wheth[illegible] [illegible]ess of adrenaline was concerned with the rise of blood sugar [illegible]rved in these three subjects. If excess of adrenaline is a fact[illegible] when emotional and physical stress are avoided, it is clear that it plays a minor rôle and this suggests that some factor other than adrenaline must be concerned in the rise of blood sugar during anæsthetic inductions in Cases 2-4.

Emotion ceases when the higher centres of the brain have been completely depressed, and when the areas of sensory co-ordination of the brain have been depressed emotional and physical stress is impossible. Since adrenaline is rapidly oxidised in the body, it is to be expected—if excess of adrenaline produced by emotional and physical stress were the only factor acting—that the hyperglycæmia would abate when anæsthetic depression was increased beyond the level of depression of the areas of sensory co-ordination of the brain: but this is not so. In Cases 2-4, when induction

to the level of complete sensory loss had been achieved and when in consequence emotional and physical stress had ceased to act, the blood sugar continued to rise as anæsthesia deepened. After 80 minutes of anæsthesia without anoxia, it was 152 milligrams per cent. in Case 2, 134 milligrams per cent. in Case 3, and 124 milligrams per cent. in Case 4. It is clear that the control of emotional and physical stress during the pre-anæsthetic period and during anæsthetic induction will materially reduce the intensity of hyperglycæmia during anæsthetic induction. It is clear, too, that emotional and physical stress is not the only factor acting to produce hyperglycæmia during anæsthesia. For the purpose of this discussion, the additional factor or factors acting during anæsthesia to produce a rise of blood sugar is termed the *residual factor.*

The blood sugar curves of Cases 2-4 during anæsthesia are strictly comparable. In each instance anæsthesia lasted for 90 minutes; efficient nursing, adequate premedication with scopolamine (gr. 1/100), and morphia (gr. 1/4), followed by a swift and trouble-free induction and maintenance with pentothal, nitrous oxide, oxygen and ether, and complete absence of oxygen lack throughout, ensured that only the residual factor was acting during induction and maintenance to produce hyperglycæmia. Moreover, these three subjects were British soldiers in an Indian Command where their diet was adequate, and, because their diet contained adequate carbohydrates, it can be assumed that liver glycogen prior to anæsthesia was not deficient. In these three cases, the level of anæsthetic depression was progressively increased throughout, to be greatest at the end of 90 minutes of anæsthesia; at the end of this period of time, anæsthesia was deepest in Case 2 and lightest in Case 4. Reference to Table 52 and Figure 17 shows that, in each instance, the blood sugar rose as anæsthesia deepened, and that the intensity of hyperglycæmia varied as the depth of anæsthesia. In Case 2, at the greatest level of anæsthetic depression the blood sugar reached a maximum of 152 milligrams per cent., which is an increase of 95 per cent. above the resting value of this subject. In Case 3, the maximum value was 134 milligrams of sugar per cent., an increase of 68 per cent.; and in case 4, the lightest anæsthetic, it rose to a maximum value of 124 milligrams of sugar per cent., which represents a rise of 48 per cent. above the resting blood sugar value of this subject. In the absence of other

factors, there is reason to conclude that the intensity of the hyperglycæmia produced by the residual factor during anæsthetic induction and maintenance varies as the depth of anæsthesia.

Reference to Table 52 and Figure 17 shows that hyperglycæmia rapidly diminishes with the cessation of anæsthetic administration. Recovery was rapid in Case 3. Here the co-operative stupor stage of recovery was reached in 30 minutes, and the blood sugar at this stage is seen to have fallen to 77 milligrams per cent. In Cases 2 and 4, recovery to this stage was slower and, when the co-operative stupor stage of recovery had been reached, the blood sugar is seen to have fallen to 88 milligrams per cent. in Case 4, and to 80 milligrams per cent. in Case 2. This behaviour suggests that the intensity of residual hyperglycæmia diminishes in parallel with the rate of anæsthetic recovery, and that, in the absence of other factors, blood sugar returns to the normal resting level when the concentration of the anæsthetic has fallen below the threshold concentration necessary to depress the cells of the central nervous system.

The return of blood sugar to its normal resting level may be delayed, however, by the glycogenolytic action of adrenaline produced by emotional and physical stress, and/or by anoxia during the period of anæsthetic recovery. In Case 2, the non-cooperative stupor stage of anæsthetic recovery was reached at 180 minutes, when it is seen that the blood sugar of this subject had fallen to 75 milligrams per cent. At this point, post-anæsthetic morphia was intentionally withheld, and the restlessness which occurred—with consequent secretion of adrenaline—is seen to have produced a rise of blood sugar at 210 minutes to 80 milligrams per cent. Anoxia was found to produce a similar result. This rise of blood sugar in Case 2 is in contrast to the corresponding recovery period of Cases 3 and 4, in which anoxia was avoided and post-anæsthetic morphia prevented post-anæsthetic restlessness: in these there was no post-anæsthetic rise of blood sugar.

Case 5 was an adequately premedicated low spinal anæsthetic for hæmorrhoids, in whom 0 8 cubic centimetres of a 5 per cent. solution of stovaine was injected intrathecally. Within ten minutes of its administration, the blood sugar of the subject had risen from its resting level of 84 milligrams per cent to 95 milligrams per cent.; at the end of surgical interference, it is seen that this level of

yperglycæmia had been maintained. In this instance, the slight ise of blood sugar is in keeping with the small mass of stovaine ixed at the site of anæsthetic drug fixation.

It can be concluded that there is a residual factor acting during næsthesia which produces hyperglycæmia, and that this factor— nd in turn the rise of blood sugar that it produces — varies in ntensity as the depth of anæsthesia. This residual factor may be ntensified by occasional factors such as anoxia, and by the excesive secretion of adrenaline during anæsthetic induction and ecovery; there may be other occasional factors. Anoxia may act hroughout anæsthesia, but the excessive secretion of adrenaline produced by emotional and physical stress acts only during anæshetic induction and recovery.

Bollman, Mann and Magath (1925) demonstrated that hyperglycæmia does not occur when the liver has been removed and Soskin (1927) has shown, when the abdominal viscera including the liver are removed, that neither epinephrine, asphyxia nor ether anæsthesia produce hyperglycæmia, in spite of the fact that glycogen was present in the muscles. Keeton and Ross (1919) observed that section of the nerves of the liver and inactivation of the adrenal glands did not abolish hyperglycæmia during anæsthesia. Phillips and Freeman (1933) confirmed these results, and showed, moreover, that complete sympathectomy in cats did not abolish the residual hyperglycæmia during anæsthesia. It can be concluded that the liver is the main source of hyperglycæmia during anæsthesia, and that glucose is released into circulating blood from the liver in amounts which depend upon the intensity of the yet-unknown residual factor.

Bollman (1929), Major and Bollman (1932), and Murphy and Young (1932) have shown that liver glycogen is depleted during anæsthesia. In cats, liver glycogen falls 50 per cent. after two hours' anæsthesia with luminal, 25 per cent. after one hour's chloroform, and 50 per cent. after one hour's ether anæsthesia. The depletion of liver glycogen is in keeping with the rise of blood sugar. In cats, ether anæsthesia lowers the liver glycogen by 15-20 per cent. in the first 6 minutes of anæsthesia, and this depletion may be reduced to 10 per cent. if the splanchnic nerves are cut. This rapid depletion of liver glycogen during anæsthetic induction coincides with the rapid rise of blood sugar seen in Case 1 of

factors, there is reason to conclude that the intensity of the hyperglycæmia produced by the residual factor during anæsthetic induction and maintenance varies as the depth of anæsthesia.

Reference to Table 52 and Figure 17 shows that *hyperglycæmia* rapidly diminishes with the cessation of anæsthetic administration. Recovery was rapid in Case 3. Here the co-operative stupor stage of recovery was reached in 30 minutes, and the blood sugar at this stage is seen to have fallen to 77 milligrams per cent. In Cases 2 and 4, recovery to this stage was slower and, when the co-operative stupor stage of recovery had been reached, the blood sugar is seen to have fallen to 88 milligrams per cent. in Case 4, and to 80 milligrams per cent. in Case 2. This behaviour suggests that the intensity of residual hyperglycæmia diminishes in parallel with the rate of anæsthetic recovery, and that, in the absence of other factors, blood sugar returns to the normal resting level when the concentration of the anæsthetic has fallen below the threshold concentration necessary to depress the cells of the central nervous system.

The return of blood sugar to its normal resting level may be delayed, however, by the glycogenolytic action of adrenaline produced by emotional and physical stress, and/or by anoxia during the period of anæsthetic recovery. In Case 2, the non-cooperative stupor stage of anæsthetic recovery was reached at 180 minutes, when it is seen that the blood sugar of this subject had fallen to 75 milligrams per cent. At this point, post-anæsthetic morphia was intentionally withheld, and the restlessness which occurred—with consequent secretion of adrenaline—is seen to have produced a rise of blood sugar at 210 minutes to 80 milligrams per cent. Anoxia was found to produce a similar result. This rise of blood sugar in Case 2 is in contrast to the corresponding recovery period of Cases 3 and 4, in which anoxia was avoided and post-anæsthetic morphia prevented post-anæsthetic restlessness· in these there was no post-anæsthetic rise of blood sugar.

Case 5 was an adequately premedicated low spinal anæsthetic for hæmorrhoids, in whom 0 8 cubic centimetres of a 5 per cent. solution of stovaine was injected intrathecally. Within ten minutes of its administration, the blood sugar of the subject had risen from its resting level of 84 milligrams per cent. to 95 milligrams per cent.; at the end of surgical interference, it is seen that this level of

due to the residual factor is not as great as could be expected from the depth of anæsthesia; in cases where liver glycogen is deficient before anæsthesia, this check in glycogenolysis is thought to be a protective reaction.

Beecher (1940) states that hyperglycæmia probably exerts a protective influence during anæsthesia, and when glycogenesis ceases during anæsthesia, owing to excessive depletion of liver glycogen, the second source of glucose—muscle glycogen—is tapped. Muscle glycogen, however, is not readily converted into glucose, and its breakdown, termed *glycolysis*, yields lactic acid which is normally converted to glycogen in the liver (the cori cycle) to be released from thence as glucose.

Ronzoni, Koechig and Eaton (1924), Hubner (1931), Fuss (1930), and others have observed an increase in the lactic content of circulating blood during anæsthesia. Adrenaline and anoxia are occasional factors which may produce glycolysis during anæsthetic induction and recovery; but, when these occasional factors are excluded, a residual increase of blood lactic acid may still be observed during anæsthetic maintenance. Eichler (1929) found that the lactic acid content of frog's muscles increased during ether anæsthesia. Ronzoni, Koechig and Eaton (1924) observed an increase in the lactic acid and phosphoric acid content of venous blood; and Stehle and Bourne (1924) found that as the phosphoric acid content of muscle decreased that of the liver increased, with an increased excretion of phosphates in the urine. Fuss (1930) asserts that the lactic acid content of circulating blood increased more rapidly during anæsthesia than does blood sugar, but it is likely that this result was complicated by the occasional factors, excitement and anoxia. The work of other observers, however, indicates that glycolysis, in the absence of other factors, is a late event in anæsthesia. Lipow, Weaner and Reid (1929) observed in dogs that an increase in blood phosphorus occurred towards the end of anæsthesia, and Marenzi and Gerschmann (1933) assert that blood phosphorus increases only after one hour of anæsthesia. These results are in accord with the observations of Bollman (1932) who found that amytal anæsthesia produced little if any decrease in muscle glycogen (and amytal anæsthesia is relatively light), while in prolonged ether anæsthesia in dogs a marked lowering of muscle glycogen was observed.

Table 52, and it is without doubt caused by excess of adrenaline produced by emotional and physical stress. Evans *et al.* (1931) have shown that when induction is complete, the depletion of liver glycogen is slowed, and this in turn coincides with the progressive steady rise of blood sugar caused by the residual factor as seen in Cases 2-4 of Table 52. These observers point out that after 60 minutes' ether anæsthesia, 50 per cent. of the glycogen content of the liver has disappeared, and that from this time onwards in anæsthesia the rate of depletion of liver glycogen is considerably slowed. When, however, liver glycogen has been depleted prior to anæsthesia by fasting or experimental procedures, the blood sugar may not rise in parallel with the depth of anæsthesia, and this may also be the case when, due to excessive emotional and/or physical stress, liver glycogen is excessively depleted during anæsthetic induction. Case 1 in Table 52 illustrates this point. In this instance, the subject's blood sugar rose from a resting level of 86 milligrams per cent., to 185 milligrams per cent. at the end of a very stormy anæsthetic induction In the absence of emotional and physical stress (and because adrenaline is rapidly hydrolysed) the blood sugar then fell to 144 milligrams per cent., which can be assumed to be the residual blood sugar level at this depth of anæsthesia. This was followed by a steady rise of blood sugar as anæsthesia deepened and the residual factor became more intense, until at length, at the greatest depth of anæsthesia attained in this subject, it was 155 milligrams per cent. Since anæsthesia in Case 1 was considerably deeper than in Case 2, one would have expected more intense hyperglycæmia at the greatest depth of anæsthesia in Case 1 than in fact occurred. The relatively low blood sugar at the greatest depth of anæsthesia in Case 1, may be attributed to the excessive depletion of liver glycogen which occurred during anæsthetic induction in this subject.

Evans *et al* (1931) observed, after 60 minutes' ether anæsthesia, when the glycogen content of the liver had been reduced by 50 per cent., that the rate of depletion of liver glycogen was then considerably slowed, and that after 5 hours of luminal anæsthesia, only a negligible fall of liver glycogen occurred. It appears when liver glycogen has fallen to a certain critical level that its further depletion is checked. Bollman (1929) states that liver degeneration follows anæsthesia in which the rise of blood sugar

wholly reject adrenaline as the cause of the residual glycogenolysis or of glycolysis occurring during anæsthesia, but it is probable during anæsthesia to the level of the complete depression of the areas of sensory co-ordination of the brain, that the secretion of insulin on the one hand, and epinephrine on the other, decreases in parallel, in keeping with the reduced metabolic rate during anæsthesia.

Himsworth (1942) has suggested that the hyperglycæmia of diabetes mellitus is a "purposeful hyperglycæmia." In anæsthesia, the increase in blood sugar, followed, if anæsthesia is sufficiently deep and prolonged, by an increase in blood lactic acid, in a subject whose insulin and epinephrine secretion is probably in keeping with the metabolic rate of the subject, may in like manner be rationalised as a purposeful reaction. Anæsthesia is characterised by the inability of neurones of the central nervous system to metabolise glucose, lactic acid, pyruvic acid and glutamic acid. Other factors being equal, the rate of utilisation of glucose and lactic acid by tissue cells varies as the concentration of these metabolites in circulating blood; and it is suggested that the residual hyperglycæmia of anæsthesia is an attempt to increase the glucose utilisation rate of central nervous tissue cells, or alternatively an attempt to reduce their sensitiveness to insulin. The utilisation of glucose and lactic acid by the neurones of the brain is, however, impossible during anæsthesia, nor is the sensitiveness of other tissue cells to insulin reduced, for, if this were so, non-nervous tissue cells would utilise the excess of glucose in circulating blood. The fact that in suitable conditions, non-nervous tissues can deal with this increased blood sugar during anæsthesia is shown by the work of Lamare (1932) and Minnitt (1932) who demonstrated that a therapeutic dose of insulin during anæsthesia reduced the anæsthetic hyperglycæmia. Wright (1942) asserts that the hyperglycæmia of anæsthesia is prevented by the administration of insulin, and this has been confirmed by Harris and Hind (1947). When the glycogen content of the liver has been reduced to about 50 per cent. of its normal value, muscle glycogen is called on, with a consequent rise in the lactic acid content of circulating blood. That this, too, is an unsuccessful attempt to increase the tissue utilisation rate of glucose is suggested by Sebening's work (1932). He observed in

The data examined suggest that during anæsthesia liver glycogen is first depleted with consequent hyperglycæmia which varies as the depth of anæsthesia; and that this is followed, when liver glycogen has been reduced to a certain critical level, by glycolysis with an increase in the lactic acid and phospheric acid content of circulating blood.

The reason for this residual increase in the glucose and lactic acid content of circulating blood during anæsthesia is not clear, and the mechanism of its production is not understood. Hyperglycæmia is unlikely to be caused by deficient glycogenesis, for Eisler and Hemprich (1932) reported that insulin insufficiency is not present during ether anæsthesia. Liver damage as a possible cause of deficient glycogenesis, except during chloroform anæsthesia cannot be seriously considered if anoxia is avoided; but it is possible, in prolonged anæsthesia when the alkaline reserve of the body has been depleted, that acidæmia may be a possible occasional contributing cause of deficient glycogenesis. On the other hand, most of the evidence indicates that glycogenolysis followed by glycolysis occurs during anæsthesia. During anæsthetic induction and recovery, excess of adrenaline produced by emotional and physical stress undoubtedly causes an increase in blood sugar and blood lactic acid, and relative anoxia throughout anæsthesia may produce the same result. It is thought by some that excess of adrenaline may be the cause of the residual hyperglycæmia and of rise of blood lactic acid which occurs when anoxia is avoided and when emotional and physical stress has ceased to act. Elliott (1912) stated that the secretion of adrenaline in cats increased during ether, chloroform and urethane anæsthesia, and that section of the splanchnic nerves diminished the output of the adrenal glands. He concluded that anæsthesia exhausts the adrenal glands, and this suggests that adrenaline is the cause of the residual glycogenolysis and glycolysis during anæsthesia. Keeton and Ross (1919) failed to confirm Elliott's work in dogs, but they are of the opinion that anæsthesia probably causes an increased production of adrenaline Kodama (1924), however, asserts that ether anæsthesia reduces the output of adrenaline by 60 per cent., and that both the concentration and the output of adrenaline increases as soon as the administration of ether ceases. In the present state of our knowledge it is impossible to accept or

increased in parallel with the depth of anæsthesia, but that this rise was a delayed one beginning about thirty minutes after the start of anæsthesia and maintained for about five hours after anæsthesia had finished. The significance of this time lag is not known, but it explains the negative findings that have occasionally been reported.

"Fats burn in the flame of carbohydrates," and in normal conditions of life, when carbohydrates are available, the end products of the metabolism of fats are carbon dioxide and water. In anæsthesia, as in diabetes mellitus, because the ability to metabolise carbohydrates is deficient, the oxidation of fat is incomplete and the products of this incomplete combustion (namely, β hydroxyl butyric acid, $CH_3CHOH.CH_2COOH$, and aceto-acetic acid, $CH_3CHO{=}CH.COOH$. — called acetone bodies) are excreted into circulating blood.

Shaffer (1924-27) has shown *in vitro* that one molecule of glucose is required for the complete oxidation of two molecules of fatty acid, and subsequent observations in Man show that acetone bodies are excreted only when the fatty acid - glucose ratio exceeds 2 : 1. According to Harrison (1943) the presence of acetone bodies in the blood stream is of little significance until more than 2 grams of total acetone bodies are excreted in the urine daily. When the FA - G ratio exceeds 2 : 1, excessive amounts of acetone bodies enter the blood stream; Lusk (1928) states that in a severe case of diabetes mellitus, the daily excretion of acetone bodies may exceed 50 grams.

When acetone bodies are present in circulating blood in significant amounts, this condition is termed a ketosis, and individuals vary very considerably in their susceptibility to ketosis. Infants, children and females — particularly pregnant women — are susceptible to ketosis more than adult males, but obese individuals on the other hand may have a FA - G ratio of 2 4 : 1 without a ketosis occurring. Cats and dogs also have a high tolerance against ketosis and they do not develop a starvation ketosis. Bodansky (1934) states that these animals can dispose of large amounts of aceto-acetic acid injected intravenously, and this fact must be remembered when assessing data obtained in experimental work on these animals.

man that 4 grams of lactic acid in the form of sodium lactate disappears from the blood stream during anæsthesia more slowly than in normal conditions of life. This suggests that the synthesis of lactic acid to glycogen in the liver—the cori cycle—is deficient during anæsthesia, and that glycogenesis decreases in keeping with the lowered metabolic rate during anæsthesia. Of even greater importance than the inability of the body to utilise this excess of the carbohydrate, lactic acid, is the fact that the concentration of the non-volatile acid, lactic acid, increases in circulating blood

When the cells of a heterogeneous cell system lose their ability to metabolise carbohydrates, or when the carbohydrate reserve of the body is deficient, the body is forced to metabolise fats in greater amounts than is normal; and, as Leathes (1925) has said, " there is a flooding of the metabolic mill with fats." The lipæmia which has been reported during anæsthesia by so many observers is attributed to this cause As in diabetes mellitus, so in anæsthesia this lipæmia cannot be accounted for solely by the demands of tissue cells for a suitable form of energy, for if this were the sole factor, fats would not continue to accumulate in circulating blood. Special significance has been attached to the cholesterol esters and the phospholipids of blood for it is thought that these compounds represent an early stage in the metabolism of fatty acids, and that in these combinations ready transportation and interchange of fatty acids between tissues is possible In any condition of lipæmia, an increase of blood cholesterol and lecithine may occur; Wright (1938) states that in diabetes mellitus, blood cholesterol increases in parallel with the severity of the disease, and is an indication of the extent to which fats are being called upon.

Many observers have shown that the rise in blood cholesterol is proportional to the depth and duration of anæsthesia and that a sudden increase in the depth of anæsthesia is followed by an abrupt rise in the cholesterol content of circulating blood. Beecher (1940) states that excitement during the non-cooperative stupor stage of anæsthetic induction produces a rise of blood cholesterol, and he attributes the sharp rise of blood cholesterol during induction with nitrous oxide and ethylene to this cause. When premedication was adequate and induction was free from excitement and anoxia, Harris and McMartin (1943) found that blood cholesterol during pentothal, nitrous oxide, oxygen and ether anæsthesia,

anæsthesia is responsible for their presence in circulating blood, and in each instance their concentration in circulating blood varies as the depth and duration of anæsthesia.

When non-volatile acids enter circulating blood, they immediately react with plasma bicarbonate in an effort to maintain the pH of circulating blood within normal physiological limits. This reaction results in the formation of basic salts and carbonic acid, which is a weak acid; and, so long as there is sufficient bicarbonate present in blood plasma, no acid stronger than carbonic acid can exist in circulating blood. In addition the epithelium of the renal tubules forms ammonia from blood amino acids, and this ammonia enters the blood stream to neutralise non-volatile acids with the formation of ammonium salts which are secreted in the urine. The ammonium mechanism has the effect of sparing the fixed bases of the blood, and non-volatile acids such as acetone bodies and lactic acid are excreted in the urine, partly in combination with ammonia and partly in combination with fixed bases.

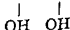
All authorities agree that there is a disturbance of the acid-base balance, with a diminution of the alkali reserve of the body during blood-borne and local anæsthesia. Reimann and Bloom (1918) concluded that acetone bodies were responsible for 60 per cent, if not all, of the diminution of alkali reserve, but Short (1920) and Kockman (1937) are of the opinion that acetone bodies alone were not sufficient to account for the diminution of the alkali reserve which occurs during anæsthesia. Fuss (1930) states that the lactic acid content of blood increases in parallel with the acidæmia produced during anæsthesia, but Ronzoni, Koechig and Eaton (1924) were unable to establish a clear relationship between the increase of blood lactic acid, and the diminution of the alkali reserve; Schmidt (1930) holds that lactic acid is not wholly responsible for the disturbed acid - base balance occuring during anæsthesia There is little doubt that acetone bodies and lactic acid are collectively the cardinal factors responsible for the diminution of the alkali reserve of the body during anæsthesia, and there may be other factors.

The alkali reserve of the body refers to the amount of base, viz., sodium, potassium, calcium, and magnesium, combined as bicarbonate, and it reflects fairly accurately the reserve of available alkali present in the whole body. Bodansky (1934)

De La Verga (1932) found a considerable increase in acetone bodies in Man during anæsthesia and Short (1920) observed a slight increase in acetone bodies after forty-five minutes' anæsthesia. Schulze (1924) states that 67 per cent. of all anæsthetics and 85 per cent. of local anæsthetics have acetonuria in the post-operative period. The present writer considers these figures too high, for in 115 consecutive anæsthetics in whom premedication was adequate and anæsthetic induction free from excitement and anoxia, acetone was found in the first post-anæsthetic specimen of urine in only 15 per cent. of cases. It might well be that excitement and/or anoxia was responsible for the very high percentage of acetonuria in Schulze's cases. Leake and Koehler (1923) and Fuss (1930) report only a slight increase in blood acetone of dogs after prolonged ether anæsthesia, but these results must be assessed in the light of the ability of dogs to dispose of large amounts of acetone bodies present in circulating blood.

It can be concluded that the lipæmia and in turn the formation of acetone bodies vary as the intensity of anæsthetic hyperglycæmia, and it follows that the degree of ketosis varies as the depth and duration of anæsthesia Occasional factors, such as emotional and physical stress, and anoxia—which accentuates the intensity of the residual hyperglycæmia—in turn increases the concentration of acetone bodies in circulating blood during anæsthesia.

β hydroxyl butyric acid is a relatively harmless substance, and in Man, constitutes about 80 per cent. of the acetone bodies normally found in the urine. Aceto-acetic acid normally amounts to about 20 per cent. of the urinary acetone bodies in Man but when present in circulating blood in large amounts—and this is unlikely in anæsthesia except in an unbalanced diabetic—it is highly dangerous, for, by reason of its enolic form — C = C —,



aceto-acetic acid stimulates breathing and depresses the brain centres with consequent coma. The ketosis which occurs during anæsthesia in Man is harmful, however, not on account of the individual pharmacological properties of acetone bodies, but mainly because acetone bodies are non-volatile acids.

Two groups of non-volatile acids enter the blood stream during anæsthesia, viz. acetone bodies and lactic acid. In each instance, the deficient carbohydrate metabolism which produces a state of

waste products of protein metabolism in transit to the organs of excretion, the kidneys, are retained during anæsthesia because of diminished urinary secretion.

Table 53, which is constructed from the observations of Pringle, Maunsell and Pringle (1905) illustrates the behaviour of ten female subjects during ether anæsthesia. During the thirty minutes before anæsthetic induction, emotional stress was responsible for a urinary secretion of 74 per cent. above their normal average half-hourly secretory rate, and emotional and physical stress during anæsthetic induction resulted in a urinary secretion of 142 per cent. above the normal resting value. With the complete anæsthetic depression of the areas of sensory co-ordination and the progressive depression of the areas of motor co-ordination of the brain, urinary secretion fell in a decisive manner. During the first half hour of anæsthetic maintenance, it fell to 23 per cent. of the resting half-hourly rate, during the second half-hour to 13 per cent., and during the third half-hour of anæsthetic maintenance, urinary secretion was virtually suppressed, for it was reduced to 3·6 per cent. of the resting average half-hourly rate.

This diminished urinary secretion has been observed during anæsthetic maintenance with all blood-borne and local anæsthetics. In blood-borne anæsthesia diminished urinary secretion is accompanied, when anæsthesia reaches the level of complete sensory loss, by a cessation of the secretion of tears, saliva, sweat, and in fact all forms of extrarenal fluid loss except the excretion of water vapour in expired air In local anæsthesia, urinary secretion diminishes as the anatomical nature of the nerve block, and in spinal anæsthesia it varies as the number of spinal segments blocked; whatever the technique of administration, it is probable that the mass of local anæsthetic absorbed into circulating blood from the site of its injection also plays a part in the reduction of urinary secretion which occurs. In each instance, urinary secretion decreases as anæsthetic depression becomes more intense. There is reason to believe that the progressive diminution of the metabolic rate of the body which occurs as anæsthesia deepens is a factor in this progressive diminution of urinary secretion, for there is a parallelism between the minute blood flow through the kidneys and the volume of urine secreted. The observations of MacNider

states that a diminution of the alkali reserve, from whatever cause, is accompanied by a definite reduction in the potassium and the sodium content of the blood, and Marenzi and Gerschmann (1933) report a 15 - 46 per cent. fall in the potassium content of blood during anæsthesia. The fall was greatest after 60 minutes' anæsthesia and was not due to a change in the plasma volume during anæsthesia. Neither of these observers, nor Lepow (1929), could detect any change of plasma sodium during anæsthesia. The diminution of plasma bicarbonate during anæsthesia should logically be followed by a chloride shift with an increase in serum chloride and Bodansky (1934) and Chabanier, Lobo-Onell and Lelu (1932) state that serum chlorine does in fact increase during anæsthesia. Beecher (1940) reports that blood magnesium decreases and Marenzi and Gerschmann (1933), Magee, Anderson and Glennie (1928) and Emerson (1928) all found a slight decrease in serum calcium during anæsthesia. Observations concerning calcium during anæsthesia are conflicting, but as Emerson suggests, a rise in blood phosphate is often accompanied by a fall of blood calcium and, as has already been seen, blood phosphates increase after sixty minutes' anæsthesia. There is little doubt that fixed bases are depleted during anæsthesia and that the alkaline reserve of the body is diminished. As the pH of blood tends to fall because of the depletion of fixed bases, the buffer reaction of phosphates becomes more important, for while the bicarbonate buffer is most efficient at pH 7 35, the buffer action of phosphates reaches its maximum efficiency at pH 6 8.

The abnormal metabolism of carbohydrates and fats during anæsthesia is in marked contrast to the metabolism of proteins.

Normally there is a limited storage of proteins in the body of an adult animal, and, if the amino acid derived from the diet is insufficient and if the supply or utilisation of carbohydrates and fats is inadequate to meet the caloric needs of the animal, the body may be forced to depend upon its own tissue proteins; at such times an excessive amount of tissue breakdown occurs Although nowadays subjects are not starved prior to anæsthesia. the abnormal metabolism of carbohydrates and fats during anæsthesia suggests abnormal protein metabolism. The data at our disposal are incomplete; if katabolism of proteins does occur during anæsthesia, it is not excessive, but there is little doubt that the

(1929) indicate that the diminution of the alkaline reserve, occurring as the depth and duration of anæsthesia increases, may be a factor in reducing urinary secretion. This factor can be expected to exert a significant influence on urinary secretion only when anæsthesia has been maintained for an appreciable length of time, and its influence may account in part for the very small volume of urine secreted during the third half-hour of anæsthetic maintenance in Table 53. Finally, it has been suggested that renal damage during anæsthesia plays a part; this is improbable but is discussed later.

The degree to which urinary secretion is depressed during anæsthesia has in the past been associated with the particular anæsthetic employed. It is said that di-ethyl ether and chloroform anæsthesia materially reduce urinary secretion, but that ethylene and nitrous oxide produce little if any suppression of urinary secretion, and this is in fact so. Di-ethyl ether and chloroform are potent anæsthetics, and deep anæsthesia with these or with any other anæsthetic agent invariably produces a marked suppression of urine. Nitrous oxide, however, is a weak anæsthetic, and the greatest depth of anæsthesia possible in an adequately oxygenated subject with this anæsthetic is insufficient to reduce significantly the volume of urine secreted. It is clear that suppression of urinary secretion occurs with all forms of anæsthesia if the level of anæsthetic depression is sufficiently intense, and the degree to which urinary secretion is suppressed varies, not as the anæsthetic agent employed, but as the depth of anæsthesia produced. When only the higher centres of the brain are depressed during blood-borne anæsthesia, or when spinal anæsthesia involves only the sacral nerve roots, the volume of urine excreted is not significantly less than the resting index for the particular subject. If the level of depression during blood-borne anæsthesia reaches or exceeds the level of complete sensory loss, water retention becomes more intense, for to the diminished secretion of urine must now be added the suppression of all other forms of extrarenal fluid loss except the excretion of water vapour in expired air. Spinal anæsthesia which reaches or exceeds the level of the sixth thoracic nerve roots materially reduces the volume of urine secreted; and when to this is added the absorption of local anæsthetic into the blood stream from the site of injection, and the premedication employed, water

TABLE 53

AVERAGE URINARY SECRETION OF 10 FEMALE SUBJECTS

	Normal resting half-hourly rate (%)	During 30 minutes prior to induction (%)	During induction	*During anæsthetic maintenance*			*During anæsthetic recovery*	
				First half-hour (%)	Second half-hour (%)	Third half-hour (%)	First six hours (%)	Next 24 hours (%)
Urinary secretion by volume	100	174	242	23	13	3 6	62	37
Urinary total nitrogen by weight	100	131	139	22	11	2 2	64	81
Concentration of urinary total nitrogen	100	85	60	101	112	104	109	135

produced by post-operative morphia and/or cardiovascular distress from hæmorrhage, surgical shock, etc., may also reduce the volume of urine secreted. It is known that under exceptional conditions of heat and/or exercise, the amount of water lost as sweat over a given period of time may readily exceed the amount of water secreted in the urine, and when in the post-operative period a diminished metabolic rate is combined with a restricted fluid intake and excessive fluid loss from extrarenal sources, it is clear that the volume of urine secreted will be small and will bear no relation to the loss of fluid by the body taken as a whole. Hence, there is reason to believe that the small volume of urine secreted during anæsthetic recovery *does not indicate water retention*, and it is the author's opinion that the kidneys regain their control of the water balance of the body early in anæsthetic recovery.

It can be concluded that diuresis and fluid loss from extrarenal sources may be excessive in the pre-anæsthetic period if premedication is inadequate, and during anæsthetic induction if this period of anæsthesia is prolonged and troublesome; moreover, that the intensity of water retention during anæsthetic maintenance varies as the depth and duration of anæsthesia, and that water retention does not occur during anæsthetic recovery.

The influence of this upset of the water balance of the body on the excretion of the waste products of protein metabolism, is illustrated by the figures shown in Table 53. Reference to this Table shows that the urinary total nitrogen excreted during the pre-anæsthetic period rose to 131 per cent., and during anæsthetic induction to 139 per cent of the average resting rate of the excretion of urinary total nitrogen for this series. This increased excretion of urinary total nitrogen can be attributed to increased metabolic activity produced by the emotional and physical stress which occurred during the pre-anæsthetic period, and during anæsthetic induction, in this series. Although the mass of total nitrogen excreted in the urine during this period was greater than the average resting rate of excretion, its concentration in the urine secreted was below the average resting concentration of urinary total nitrogen for the series. For example, during anæsthetic induction, when the volume of urine secreted was 142 per cent. in excess of the average resting rate, the mass of urinary total nitrogen excreted was 39 per cent above the resting rate of excretion, but

retention of considerable intensity can be expected during this level of spinal anæsthesia. In all forms of surgical anæsthesia, if the duration of anæsthesia exceeds about one hour, the gradual diminution of the alkaline reserve of the body which inevitably occurs may produce a diminution in the volume of urine secreted

It has been seen that the water retention of natural sleep is followed by a compensatory increased secretion of urine on awakening. In the absence of factors other than a diminished metabolic rate, it is to be expected that the water retention during anæsthetic maintenance should be followed in the post-anæsthetic period by a compensatory increased secretion of urine. Hawk (1911) observed in dogs that the water retention of ether anæsthesia was followed in the post-anæsthetic period by a diuresis of 5 - 25 per cent. This post-anæsthetic diuresis, however, is seldom observed in clinical anæsthetic practice in Man. In the series shown in Table 53, 120 c.c. of urine were secreted during the first six hours of anæsthetic recovery—equivalent to 62 per cent. of the normal average secretory rate for this period of time. During the next twenty-four hours 431 c.c. of urine was secreted—equivalent to 37 per cent. of the average daily rate of secretion for this series. Recent observations give slightly higher values, for when minor operations are excluded, ward records show that about eight ounces (227 c c) of urine are secreted in the first twelve hours of anæsthetic recovery, and about one pint (568 c.c.) of urine during the next twenty-four hours.

These figures suggest water retention during the post-anæsthetic period, but there are many factors responsible for this subnormal secretion of urine during anæsthetic recovery. On the one hand, fluid intake may be restricted in the post-operative period by vomiting and/or for surgical reasons, and, on the other hand, extrarenal sources of fluid loss may be augmented during the post-operative period. Thus, as soon as the subject's ability to react to external stimulus returns, all those glands that react to external stimulus commence to secrete, and if the non-cooperative stupor stage of anæsthetic recovery has been violent and prolonged, the secretion of lacrimal, salivary, bronchial, and sweat glands may be excessive, while vomiting may introduce another occasional source of serious fluid loss. In addition to this diminished fluid intake and increased extrarenal fluid loss, a diminished metabolic rate

anæsthesia. Bich (1930) has observed in dogs, and Inami (1931) in rabbits, a rise in the N.P.N. content of blood during ether anæsthesia.

Urea represents about 50 - 60 per cent. of the N.P.N. content of blood, and about 80 - 90 per cent. of the total nitrogen content of urine. It is formed by the de-amination of amino acids in the liver, and once formed, is not destroyed in the body but is excreted unchanged in the urine by the kidneys. It is only in the most severe forms of liver degeneration that interference with liver function is sufficiently gross to upset the normal metabolism of amino acids and the formation of urea. Rabonowitch (1929) reported a fatal case of acute yellow atrophy of the liver of unknown origin with renal degeneration and anuria, in which the amino acid content of blood increased to 216 mgs. per cent., and its urea content fell to zero.

Blood amino acids are not significantly altered during anæsthesia. Ross (1918) records a slight fall in the amino acid content of blood after fifteen minutes' ether anæsthesia and in clinical anæsthetic practice no alteration or a slight progressive fall of blood amino acid values is generally observed as anæsthesia proceeds. This can be attributed to a diminished rate of absorption of amino acids from the intestinal tract combined with their continued de-amination in the liver during anæsthesia. The writer has observed a rise of blood amino acid values only once during anæsthesia. It occurred in a subject with intense obstructive jaundice of six weeks' duration in whom liver inefficiency was suspected and the gradual rise of blood amino acid values which occurred during eighty minutes' anæsthesia with nitrous oxide, oxygen, di-ethyl ether and d-tubo-curarine chloride, is seen in Table 54. This effect can be attributed to a reduced ability to utilize blood amino acids when liver inefficiency is present but the order of the rise of blood amino acids in this subject indicates that the de-amination of amino acids is not significantly affected during clinical anæsthesia unless severe liver degeneration is present.

It has been generally observed that blood urea values rise in keeping with the depth and duration of anæsthesia in a manner similar to that of the case shown in Table 54. King-Li-Pin and Woo-Ping-Soung (1934) observed a rise of blood urea during chloroform, ether and urethane anæsthesia Shackle (1932)

its concentration in the urine secreted fell to 60 per cent. of the resting concentration for the series. This illustrates the fact that the individual constituents of urine are largely though not entirely independent of one another as regards the rate of their excretion from blood to urine.

During anæsthetic maintenance, it is seen that the mass of urinary total nitrogen fell in strict parallel with the diminished secretion of urine which occurred as the depth and duration of anæsthesia increased. During the first half-hour of anæsthetic maintenance, the mass of total nitrogen excreted in the urine was 22 per cent. of the resting value, and its concentration in the urine secreted was of the same order as the average resting concentration of urinary total nitrogen for the series. During the second half-hour, the mass of urinary total nitrogen excreted fell to 11 per cent., and during the third half-hour of anæsthetic maintenance it fell to 2·2 per cent. of the average resting rate of excretion for this series. In each instance, its concentration in the urine secreted was slightly greater than the average resting concentration of urinary total nitrogen for this series. Since extrarenal sources of nitrogen excretion cease during anæsthetic maintenance, it can be concluded that the excretion of total nitrogen is virtually suppressed during anæsthetic maintenance; the figures in Table 53 indicate that water retention during this period is a major factor in producing the diminished excretion of total nitrogen, for the solids of urine demands a certain minimum volume of water, a certain *volume obligatoire*, for their excretion in the urine.

Urinary total nitrogen consists of the nitrogen content of the urea, amino acids, uric acid, creatinine, ammonia and certain undetermined substances such as hippuric acid and purine bases which are excreted from the blood streams by the kidneys in the urine. These nitrogenous substances constitute the non-protein nitrogen (or N.P.N.) content of blood and with the exception of amino acids, they represent the waste products of protein metabolism in normal conditions of life. The rate of excretion of these substances from circulating blood by the kidneys in the urine is one of the most important means of regulating their blood concentration. The diminished excretion of urinary total nitrogen produced by water retention during anæsthesia results in the retention and gradual accumulation of N.P.N. in blood during

of proteins during anæsthesia is in part responsible for the rise of blood urea. As carbohydrate metabolism is inhibited during anæsthesia, the utilisation of proteins as a source of carbohydrates is possible; in this instance, amino acids would be converted partly into urea, and the residue partly into glucose and partly into acetone bodies. Thus, excessive katabolism of tissue proteins could account in part for the increase of blood sugar, the increase of blood acetone bodies, and the increase of blood urea, all of which occur during anæsthesia. Confirmation of protein katabolism during anæsthesia is lacking, but during anæsthesia in protein depleted or asthenic subjects, or in untreated or unbalanced diabetics, it is a possibility which cannot be ignored. In normal subjects, however, the fall of blood amino acids during anæsthesia is slight and of little significance, and the oxidation of at least one amino acid—glutamic acid—is inhibited during anæsthesia.

The blood content of the remaining waste products of protein metabolism during anæsthesia have not been investigated in detail, but Hawk (1908) reports that, with the exception of hippuric acid, there is an increased excretion of these waste products in the urine during the immediate post-anæsthetic period.

Hawk (1908) observed that the excretion of uric acid is increased after chloroform anæsthesia. The endogenous source of uric acid is the breakdown of nucleoproteins; it is excreted in the urine in combination with sodium, potassium, and ammonia in the form of urates. Water retention during anæsthesia with a compensatory increased excretion of uric acid may be the only factor responsible. It is significant that, when extrarenal fluid loss is excessive, the excretion of urates in the urine is greatly increased; but Lennox (1925) believes that uric acid retention is in some way associated with ketosis.

Hawk (1908), Howland and Richards (1909) and Lindsay (1911) report increased excretion of creatinine in the urine in the immediate post-anæsthetic period Creatine, which is the immediate precursor of creatinine, is a product of endogenous protein metabolism, and in the normal adult male is converted completely into creatinine which is then excreted in the urine. Creatinine is, therefore, to be regarded as a waste end-product of endogenous protein metabolism, particularly of muscle metabolism, for most of the body's creatine is found in muscle as phosphocreatine. In

reported a rise of blood urea during ether anæsthesia, and Hewer (1946) has stated that a slight rise of blood urea occurs during barbiturate anæsthesia. The author has observed a slight progressive rise of blood urea during spinal anæsthesia, but Minnitt (1933) found no rise of blood urea during nitrous oxide anæsthesia.

TABLE 54.

Duration of Anæsthesia	Blood Sugar	Blood Urea	Blood Amino Acids
– 3 minutes	83 mgs %.	29 mgs. %.	10·5 mgs. %.
+ 10 minutes	89 mgs. %.	31 mgs. %.	11 3 mgs. %
+ 55 minutes	109 mgs. %.	39 mgs. %.	11 9 mgs. %.
+ 85 minutes	113 mgs %	43 mgs %	12 1 mgs %.

Normal blood amino acid values with a rise of blood urea suggests *normal production of urea during anæsthesia with* a retention of urea in circulating blood due to water retention. It has been observed by Harris and Hind (1947) that the rise of blood urea occurs in parallel with the rise of blood sugar, as shown in Table 54, and it can be inferred that the fall of blood amino acids, the rise of blood urea, and the rise of blood sugar vary as the depth and duration of *anæsthesia. This, in turn,* implies that the utilisation of blood amino acids and the formation of urea vary as the metabolic rate of the subject during anæsthesia, and the rise of blood urea depends upon the rate of its formation coupled with the intensity of water retention. Because nitrous oxide is a weak anæsthetic, its effect on renal excretion is slight and *the relatively minor degree of water retention during* nitrous oxide anæsthesia is the probable explanation of Minnitt's results.

The behaviour of blood amino acids and blood urea, the major waste product of protein metabolism, suggests normal protein metabolism in keeping with the metabolic rate of the subject during anæsthesia; water retention might therefore be regarded as the *dominant—probably the only—factor concerned* with the rise of blood urea during anæsthesia Beecher (1940), however, concludes that water retention does not wholly account for the rise of blood urea during anæsthesia and this infers that increased katabolism

discussed later, is probably responsible for the minor degrees of metabolic upset which occur in such subjects in the post-anæsthetic period.

Thus, the character of the physiological and metabolic upset produced by the dominant pharmacological action of anæsthetics in Man follows a definite pattern. There is a diminution of the metabolic rate, a disturbed water balance with water retention, and a retention of the N.P.N. constituents of blood; these disturbances, which vary as the level of depression of the brain, are not peculiar to anæsthetic depression but are produced when the brain is depressed to a comparable level by any agent. To these are added disturbances peculiar to anæsthetic depression alone. They consist of a hyperglycæmia, a lipæmia and a ketosis, with a diminution of the alkaline reserve of the body; the intensity of these disturbances varies as the degree of inhibition of the carbohydrate metabolism of the brain necessary to produce the given level of anæsthetic depression.

During the stage of anæsthetic sleep, the level of depression of the brain corresponds with that of light natural sleep, and the degree of upset produced coincides with the diminution of metabolism, water retention, and retention of N.P.N. expected during light natural sleep, together with a ketosis of relatively minor intensity. It has been seen that there is a compensated acidæmia of a very minor degree during natural sleep, and it can be concluded that anæsthetic sleep differs from natural sleep of comparable depth in the presence of an inevitable ketosis of minor intensity. During anæsthesia to the level of complete sensory loss, the diminution of metabolism, water retention and retention of N.P.N corresponds with a level of depression only slightly greater than that of deep natural sleep; but ketosis is more intense and consequently the upset of metabolism during anæsthetic maintenance, and in the post-anæsthetic period, is correspondingly greater.

Anæsthesia to the level of depression of the areas of motor co-ordination of the brain has no parallel in normal conditions of life. This level of anæsthetic depression results in a considerable lowering of the metabolic rate, an almost complete water retention with, in consequence, almost complete retention of the N.P.N. constituents of blood; to these must be added—if this level of

many conditions of deficient carbohydrate utilisation, in fevers, starvation, etc., an excessive amount of creatine is excreted as such in the urine, for efficient carbohydrate oxidation is essential for the complete conversion of creatine to creatinine; but, in the absence of increased protein katabolism, the output of creatine plus creatinine is equivalent to the amount of creatinine which would have been excreted if carbohydrate utilisation had been efficient and conversion complete. The absence of creatine in the post-anæsthetic period indicates that the carbohydrate metabolism of muscle is efficient during anæsthesia, and the increased excretion of creatinine in the post-anæsthetic period indicates efficient conversion with retention during anæsthesia owing to water retention. In the light of our present knowledge, the behaviour of creatinine indicates retention rather than increased protein katabolism during anæsthesia.

Bodansky states that the ammonia which is formed during the deamination of amino acids is converted almost quantitatively into urea and the normal ammonia content of circulating blood is small. Nash and Benedict (1929) observed during nephrectomy that there was no change in the ammonia content of blood, although other N.P.N. constituents of blood were retained. Ammonia elimination is increased by acidæmia and is diminished when alkalæmia is present; whatever the part it plays in the neutralisation of acids, this may be related to kidney function, which has been seen to be depressed in keeping with the depth and duration of anæsthesia. In like manner, the formation of hippuric acid, which is thought to be synthesized by the kidneys, is diminished during anæsthesia.

The evidence reviewed, which is neither conclusive nor complete, indicates that in normal subjects protein metabolism is diminished during anæsthesia in keeping with the metabolic rate of the subject. and that the waste products of protein metabolism are retained because of water retention during anæsthesia. If this is in fact a true picture, the rise of blood urea during anæsthesia can have little significance, *for uræmia is due not so much to the retention of urea* and other N.P N. constituents of blood as to the accumulation of acid, which is probably the most poisonous of all the waste products of metabolism. In carbohydrate- and/or protein-depleted subjects, however, it is probable that protein katabolism of a minor degree occurs during anæsthesia; this aspect of anæsthesia, which is

obvious way of reducing the intensity of ketosis is to reduce the level of anæsthetic depression, and as has been seen during the discussion on d-tubo-curarine chloride, there is a body of anæsthetic opinion inclining to the use of anæsthesia lighter than complete sensory loss, with repeated appropriate doses of d-tubocurarine chloride as often as is required to maintain an efficient anæsthetic preparation. This technique, however, introduces the probability of bronchospasm and other reflex effects such as cardiovascular reflexes which, though normally designed to protect, may react in an excessive and exaggerated manner during anæsthesia lighter than complete sensory loss, and such reflex effects may endanger the life of the subject. And the complications which have to date been reported during curarisation may be attributed directly to dangerously light anæsthesia, for they have not been encountered during curarisation in subjects whose ability to react to other than proprioceptive stimulus has been abolished by anæsthesia to the level of complete sensory loss. It has been concluded that the first duty of the anæsthetist is to produce a safe anæsthetic preparation which satisfies the requirements of the proposed surgical interference; this condition fulfilled, the intensity of ketosis should then—and only then—be reduced to minimal proportions. If this premise is accepted, the reduction of ketosis at the expense of safety would appear to be an irrational procedure: it is certainly dangerous.

An alternative method of approach to this problem is to postulate that safe anæsthesia cannot be maintained at a level of anæsthesia lighter than the level of complete sensory loss, and therefore to attempt to eliminate the ketosis produced by anæsthesia to this level of depression by other means. Harris and Hind (1947-48) have used a balanced dose of insulin and glucose as a pre-anæsthetic medicant in a small series of cases in which anæsthesia lasted more than two hours, but their results were inconclusive. The control of ketosis with the intravenous administration of insulin and glucose during anæsthesia shows promise of better results. Finally, the sulphur-containing amino acid—methionine—is being used as a pre-anæsthetic medicant in an attempt to reduce protein katabolism during anæsthesia to minimal proportions.

anæsthetic depression is maintained for more than about one hour —considerable interference with the return of venous blood to the right heart. Moreover, the inhibition of the carbohydrate metabolism of the brain, which is necessary to produce this level of anæsthetic depression, results in a ketosis of considerable intensity. In consequence of this, anæsthesia to this level if maintained too long inevitably results in cardiovascular distress and acidæmia both during anæsthetic maintenance and in the post-anæsthetic period. At this level of anæsthesia cardiovascular distress of this origin is a very real danger, but may be effectively neutralised by intravenous therapy with plasma or whole blood, combined with adequate oxygenation. The intensity of the ketosis, however, cannot be diminished if this level of anæsthesia is maintained, and it is the inevitable price which must be paid for anæsthesia of this depth.

Nothing illustrates the influence of ketosis during anæsthetic maintenance and *in the post-anæsthetic period* so well as a comparison of the clinical condition of a subject during and after a total gastrectomy performed, on the one hand during inhalation or high spinal anæsthesia, and on the other during inhalation anæsthesia to the level of complete sensory loss with d-tubocurarine chloride in appropriate dosage. In each instance, the *diminution of the metabolic rate,* water retention, retention of N P.N. and diminished venous return to the right heart are of the same order of intensity. In the former, ketosis during spinal anæsthesia is less than during inhalation anæsthesia, but in each instance it is intense, and even when anoxia is avoided and intravenous therapy is effective, the clinical condition of the subject after about one and a half hours of anæsthesia often gives rise to anxiety and continues to do so for the next three or four days of the post-anæsthetic period In the latter, however, ketosis is of relatively minor intensity, and when anoxia is avoided and intravenous therapy is used with clinical acumen, the clinical condition of the subject, even during anæsthesia prolonged for five hours seldom occasions alarm, and the metabolic upset in the post-anæsthetic period is reduced to a degree which must be seen to be believed.

But it is the aim of the anæsthetist to eliminate even minor degrees of ketosis during clinical anæsthesia. There are two possible lines of approach to the solution of this problem. The most

46. LINDSAY, D. E. (1911). *Bio. chem. J.* **5**, 407.
47. LIPOW, E., WRANER, W. K., and BRAD, C. I. (1929). *Amer. J. Physiol.* **90**, 432.
48. MACNIDER, W. DE B. (1929). *J. Pharmacol.* **35**, 31.
49. MAGEE, H. E., ANDERSON, W., and GLENNIE, A. E. (1928). *Brit. exp. Path.* **9**, 119.
50. MAJOR, S. G., and BOLLMAN, J. L. (1931-32). *Proc. Soc. exp. Biol. N.Y.* **29**, 1109.
51. MARENZI, A. D, and GERSCHMANN, R. G. (1933). *C.R. Soc. Biol. Paris.* **113**, 475. **114**, 1226.
52 MINNITT, R. J. (1932). *Proc. R. Soc. Med.* **26**, 347.
(1933). *Brit. med. J.* **1**, 160.
53 MURPHY, G. E., and YOUNG, F. G. (1932). *J. Physiol.* **76**, 395.
54 PHILLIPS, R. A., and FREEMAN, N. E. (1933-34). *Proc. Soc. exp. Biol. N.Y.* **31**, 286.
55. PRINGLE, H., MAUNSELL, R. C. B., and PRINGLE, S. (1905). *Brit. med. J.* ii, 542.
56. RABINOWITCH, I. M. (1929). *J. biol. Chem.* **83**, 333.
57. REIMANN, S. P., and BLOOM, C. H. (1918). *J. biol. Chem.* **36**, 211.
58. RONZONI, E, KOECHIG, I., and EATON, E. P. (1924). *J. biol. Chem.* **61**, 465.
59. ROSS, E. L. (1916) *J biol. Chem.* **27**, 45.
60. SCHMIDT, H. (1930). *Schmerz. Narkose. usu.* **3**, 209.
61. SCHULZE, F. (1924) *Zbl. Chir.* **51**, 2688.
62. SEBENING, W. (1932). "Current Researches in Anæsthesia." **11**, 145.
63 SHACKLE, J. W. (1932). *J. Clin. Med. Oct.* p. 138.
64 SHAFFER, P. A., and FRIEDEMANN, T. E (1924). *J. biol Chem.* **61**, 585.
65. SHEPARD, J. F. (1914). "The Circulation and Sleep." Macmillan, New York.
66. SHORT, J. J. (1920). *J. biol Chem* **41**, 503.
67. SOSKIN, S. (1927). *Amer. J. Physiol.* **81**, 382.
68. STEHLE, R. L., and BOURNE, W. (1924). *J. biol. Chem* **60**, 17.
69 WRIGHT, S. (1942). "Applied Physiology," 7th Ed. p. 660. Oxford University Press, London.
70 ZUCKER, T. F., NEWBURGER, P. G., and BERG, B. N. (1931) *Proc. Soc. exp. Biol. N.Y.* **29**, 294.

References.

1. Aron (1923). *Mochr. Kinderheilk.* **26**, 209.
2. Beecher, H. K. (1940). "The Physiology of Anesthesia." p. 235, 247. Oxford University Press, New York.
3. Benedict, F. G (1915). *Carnegie Inst. Washington Pub.* 203.
4. Benedict, T P., and Nash, E M. (1929). *J. biol Chem.* **82**, 675
5. Bich, A. (1930). *Arch. Ital. Chir.* **25**, 691.
6. Boas, E P (1932-33). *Amer. Heart J.* **8**, 24
7. Bodansky, M (1934) "Introduction to Physiological Chemistry." 3rd Ed p. 270, 368. J. Wiley & Son, New York.
8. Bollman, J. L (1929) *Proc. Mayo Clin.* **4**, 369.
9. Bollman, J L., Mann, F. C., and Magath, T. B. (1925). *Amer. J. Physiol* **74**, 238
10. Chabanier, H C., Lobo-O'Nell and Lelu, E. (1932) *C R. Soc. Biol. Paris.* **110**, 1282
11. Collip, J B (1920) *J biol. Chem* **41**, 473.
12. Cooper, E A , and Woodhouse, D L. (1923). *Bio. chem. J.* **17**, 600.
13. Cooperman, N. R (1936) *Amer. J. Physiol.* **116**, 531.
14. De la Verga, J. F. (1932) *Ann Acad med. quir. espan* **18**, 75
15. Ebbecke (1926). *Handbuch der Normalen und Pathologischem Physiologie* Berlin. **17**, 563.
16. Eichler, O. (1929). *Narkose a Anaesth.*
17. Eisler, B , and Hemprick, R (1932). *Z. ges exp. Med* **83**, 439.
18. Elliot, T. R (1912). *J. Physiol* **44**, 374.
19. Emerson, W. C (1928). *J Lab clin Med.* **14**, 159
20. Evans, C L , Tsai, C , and Young, F. G. (1931) *J. Physiol.* **73**, 67.
21. Fuss, H (1930) *Z ges exp. Med* **73**, 532
22. Gollwitzer-Meier, K , and Kroetz, C (1924). *Biochem. Z.* **154**, 82.
23. Grollman, A. (1930) *Amer. J Physiol.* **95**, 274.
24. Harris, T A. B , and Hind, A. W. (1946-48) Unpublished.
25. Harris, T A. B , and McMartin, R B (1943) Unpublished.
26. Harrison, G A. (1947) "Chemical Methods in Clinical Medicine" 3rd Ed. Churchill, London
27. Hawk, P. B (1911) *Arch. intern Med.* **8**, 39
28. Hertzog, R A , and Betzel, R. (1911) *Hoppe Sezl. L* **74**, 221.
29. Hewer, C L (1946) "Recent Advances in Anæsthesia and Analgesia" p 126 J. & A Churchill, London
30. Hill, A V. (1898). *Lancet,* **i**, 282
31. Himsworth, H P *Quote from* Wright, S (1942) "*Applied Physiology,*" p 657 Oxford University Press, London.
32. Hopkins, H (1935-36). *Amer J Psychiat* **92**, 75
33. Howland, J , and Richards, A N (1909) *J. exp. Med.* **11**, 344
34. Hubner, H (1931) *Inaug Dissert. Bonn*
35. Inami, R (1931) *Tohoku J. exp Med* **17**, 39
36. Keeton, R W , and Ross, E L (1919) *Amer J Physiol.* **48**, 116.
37. King-Li-Pin and Woo-Ping-Soung (1934) *C R. Soc Biol. Paris* **115**, 55.
38. Kleitman, N (1929) *Physiol Rev* **9**, 624
39. Kockman, M (1936) *Handbuch der Experimentellen Pharmakologie. Vierter band* Julius Springer, Berlin
40. Kodama, S. (1924) *J. exp Med* **4**, 601
41. Kunze, J (1928) *Z ges exp Med.* **59**, 248
42. Lamare, J P. (1932) *Brit med J.* **ii**, 52
43. Landis, E M (1925) *Amer J Physiol* **73**, 551. (1927) *Amer. J Physiol.* **81**, 6.
44. Leake, C. D., Leake, E. W , and Koehler, A E. (1923). *J. biol Chem.* **56**, 319.
45. Leathes, J B (1925) "The Fats," 2nd Ed Longmans, Green & Co London.

in certain circumstances chlorinated fatty hydrocarbons (such as chloroform in the concentrations used in clinical practice) produce protoplasmic degeneration of the myocardium, the liver and the kidneys; the aromatic series produces changes in the hæmatopoietic system, the mucous membrane of the pulmonary tract is irritated, slightly by di-ethyl ether and markedly by the aldehydes; the nitrite compounds of the inorganic oxy-acids produce intense nitrite effects; certain local anæsthetics (such as alpha eucaine) are tissue irritants, and in general the higher members of the aliphatic and cyclic hydrocarbon series are cerebral convulsants and cardiac depressants. Such side-actions produced by specific radicals in the molecule of the particular narcotics cannot be neutralized or avoided when these narcotics are used in clinical practice.

Finally, the sequence of absorption of narcotics with an oil/water partition coefficient of less than unity results in the early depression of the vital medullary centres when these narcotics are pushed; and when overpressure is used with anæsthetics with a high oil/water partition coefficient, cardiac arrythmias and/or primary cardiac failure of local origin may occur.

The dominant action of a narcotic suitable for use in clinical anæsthetic practice is the depression of the body in the standard sequence; it is clear that the fewer side-actions of a narcotic, the more valuable will it be in clinical anæsthetic practice. Clinical selection has discarded—and continues to discard—not only those narcotics that produce a distorted sequence of depression of the body but also those having deleterious side-actions. It is proposed to discuss the effects of anoxia and the dominant action of the anæsthetics in common clinical use, together with the effects of any side-action that these anæsthetics may have upon the individual organs and systems of the body

The Central Nervous System. The only store of oxygen in Man's body is the oxygen content of alveolar air, and this storage capacity is very limited. Of all the cells of the body, nervous tissue cells are least capable of withstanding oxygen lack. Astley Cooper, as early as 1836, produced anoxia of the brain by the occlusion of its blood supply; and anæmic anoxia, produced by circulatory arrest, has since been used by many observers as a means of investigating the effects of oxygen lack on the central

CHAPTER XXVI

THE DOMINANT ACTION AND THE SIDE-ACTIONS OF ANÆSTHETICS ON INDIVIDUAL ORGANS AND SYSTEMS

WHEN the standard sequence of depression obtains in clinical anæsthetic practice, it can be inferred from the preceding discussion that the concentration of the anæsthetic in each and every organ of the body except the brain is below the minimum threshold concentration necessary to depress it. If, therefore, narcosis were the sole action exercised by anæsthetics, organs and systems of the body other than the brain could not be depressed by the anæsthetic *per se*. As has been seen, the functional activity of non-nervous tissues is reduced in keeping with the level of anæsthetic depression of the brain and in turn that of the body as a whole, and may be modified by the degree of ketosis produced. These effects on organs and systems other than the brain are common to the state of anæsthesia and vary in intensity with the depth and duration of anæsthesia. They are manifestations of the dominant action of anæsthesia in a heterogeneous cell system and are not side-actions of the particular anæsthetic.

It has been assumed in this discussion that adequate oxygenation of the subject was present throughout anæsthetic induction, maintenance and recovery; but, in clinical anæsthetic practice, errors and accidents of administration sometimes produce inadvertent anoxia of varying intensity and duration. Moreover there are still some anæsthetists who believe that a relative degree of anoxia during anæsthesia is justifiable; finally, during animal experiments, anoxia is a factor sometimes not sufficiently assessed. For these several reasons anoxia is sometimes a side-action of anæsthesia and will be treated as such in this discussion.

In the concentrations used in clinical anæsthetic practice, however, certain narcotics not only produce anæsthesia but also specifically modify the functional activity of certain organs and systems in a manner quite unrelated in narcosis. For example,

in the cerebral cortex and the basal ganglia—in fatalities following nitrous oxide anæsthesia in Man. These fatal results and the lesions observed are to be attributed directly to oxygen lack. It can be concluded that oxygen lack during anæsthesia is never beneficial and always exerts a deleterious action on the cells of the central nervous system.

A relative degree of anoxia early in anæsthesia may produce jactitations, and generalized clonic movements of striated muscles are also produced in adequately oxygenated subjects by the higher members of the hydrocarbon series of narcotics. They may occasionally occur in adequately oxygenated subjects with the blood-borne and local anæsthetics in common clinical use when a depth of anæsthesia approaching overdose, is maintained. In each instance, this generalized cerebral convulsion has been attributed to an excessive release of acetylcholine (ACh) at central synapses.

The jactitations of early anæsthesia are attributed solely to asphyxia, for they are rapidly ablated by adequate oxygen in the anæsthetic atmosphere. They exhaust the subject, but seldom do else. The cerebral convulsions produced by the higher narcotic hydrocarbons are a deleterious side-action of these compounds and they are clearly unsuitable for use in clinical anæsthetic practice, for cerebral convulsions of this origin may result in the death of the subject. The idiopathic convulsions which have been reported with di-ethyl ether and most other anæsthetics in common clinical use have been attributed to a variety of causes. They occur most commonly in toxic subjects maintained at a deep level of anæsthetic depression; and if the excessive release of ACh at central synapses is, in fact, the cause of these convulsions, then toxæmia might well act synergically with deep anæsthesia to produce this result. Payne (1936) states that the mortality after idiopathic convulsions during di-ethyl ether anæsthesia is 23 per cent. During local anæsthesia, cerebral convulsions are a manifestation of overdose and when they occur, the subject is in the gravest danger. Finally, permanent nerve injury may follow an otherwise uneventful spinal anæsthetic, and evidence has been discussed which suggests that these effects may follow the use of too highly concentrated solutions of the local anæsthetics commonly used to produce spinal anæsthesia.

It can be concluded that the excessive release of ACh at central

nervous system. Gomez and Pike (1909) reported that the susceptibility of the cells of the central nervous system to oxygen lack, as indicated by histological changes produced by total anæmia, was of the order: the small pyramidal cells, Purkinji cells, the cells of the medulla, cells of the retina, cells of the cervical cord, cells of the lumbar cord and finally the cells of the sympathetic ganglia. Weingerger *et al.* (1940) observed that severe and permanent pathological change in the cerebral cortex of cats is produced by circulatory arrest of about three minutes and that Purkinji cells and those of the basal ganglia require longer periods of anæmic anoxia to produce comparable lesions. Gildea and Cobb (1930) found that the third and fourth layers of the cerebral cortex were most readily affected by oxygen lack. (Hence, anoxia is a rapid and a very potent poison to brain cells.) Sudden and complete oxygen lack produces loss of consciousness in mammals within three to eight minutes of its onset; a reduction or the total abolition of oxidative processes of living cells produced by anoxia is, moreover, an irreversible process which produces, according to its intensity, severe or permanent pathological changes The most susceptible cells, those of the cerebral cortex, are most readily affected. Then other nervous tissue cells are depressed in the standard sequence of depression and, finally, non-nervous tissue cells.

Because of the saving action of succinate metabolism, anæsthetics are not tissue poisons, and, in a properly conducted anæsthetic, they depress the central nervous system in the standard sequence. Hence, as long as the vital medullary centres are not depressed and anoxia is avoided throughout, the cells of the central nervous system recover completely when the anæsthetic is withdrawn, for its action is freely reversible. The synergism of anoxia with anæsthesia (and the fact that the action of severe anoxia is irreversible) constitutes one of the gravest dangers of clinical anæsthesia. But wittingly or unwittingly. simple asphyxiation often occurs in clinical practice with weak anæsthetics such as nitrous oxide or ethylene, when a greater depth of anæsthesia is demanded of these anæsthetics than is in their power to provide in the conditions which obtain in clinical practice. Gomez and Pike (1909), Lowenberg, Waggoner and Zbinden (1936), and Courville (1938) have all reported lesions of the brain—particularly

cats one-sixth of the increase in blood volume, or about one-third of the increased number of erythrocytes, can be attributed to erythrocytes expressed from the spleen into circulating blood. The spleen is about 1 per cent. of the cat's body weight, while the human spleen is only about 0·3 per cent. of the body weight; it is unlikely that splenic contraction, even if this had in fact been demonstrated in Man, could account for the rise in the erythrocyte count occurring when Man is subjected to relative degrees of anoxia at high altitudes. The increase in reticulated red blood corpuscles and blood platelets at high altitudes in Man suggests that red bone marrow is stimulated to increased activity by relative anoxia; Van Liere (1943) concludes that overactivity of red bone marrow produced by anoxia is probably a major factor in the production of polycythæmia at high altitudes. Van Leire doubts whether loss of plasma volume occurs and, while admitting that it may be a factor in the rise of the number of erythrocytes in blood at high altitudes, he concludes that it cannot be a major factor.

The blood changes produced by the relative anoxia of high altitudes may be rapidly induced, for Gregg, Lutz and Schneider (1919) showed that hæmo-concentration occurred in aviators within fifteen to twenty minutes of leaving the ground. In 78 per cent. of men subjected to an oxygen partial pressure equivalent to an altitude of 15,000 - 18,000 feet produced in about 15 minutes, the erythrocyte count and the hæmoglobin content of blood increased within 30-60 minutes. There is little doubt therefore that anoxia may be an occasional factor in the production of the blood changes during anæsthesia.

It has been concluded that the uptake of anæsthetics by blood is a differential solubility process, and the proportion of an anæsthetic dissolved in plasma and corpuscles varies as the oil/water partition coefficient of the particular anæsthetic. With anæsthetics such as acetylene, the ethers and nitrous oxide whose oil/water partition coefficient is low, the anæsthetic content of plasma is greater than the corpuscular content and the reverse is true of anæsthetics such as ethylene, cyclopropane, chloroform and trichlorethylene, whose oil/water partition is high. There is still doubt whether anæsthetics combine with hæmoglobin. Most observers agree that acetylene does not unite with hæmoglobin, and this may be due to this anæsthetic's relative insolubility in the

synapses with cerebral convulsions may be produced during anæsthesia by asphyxia and/or by too great a concentration of blood-borne or local anæsthetics in the cells of the central nervous system. It is probable that the permanent nerve injuries which occasionally follow spinal anæsthesia are caused by the use of too highly concentrated solutions of local anæsthetics. But, when the anæsthetics in common clinical use are administered in a proper fashion, they depress the central nervous system in the standard sequence, and the effect is freely reversible when the anæsthetic is withdrawn.

Blood, Blood Volume and Spleen. The effect of the partial anoxia observed at high altitudes has held the attention of physiologists since Paul Bert (1878) foretold that the blood of animals and men living at high altitudes would have a greater oxygen-carrying capacity than that of those living at lower levels, and our knowledge of the effect of anoxia on the blood is fairly complete and definite.

Meyer, Seevers and Beatty (1935) concluded that anoxia produced a leucocytosis, and that this was followed by a leucopænia. There is considerable evidence that large lymphocytes increase their number at the expense of polymorpholeucocytes, but in general the total white count does not materially change.

At high altitudes there is an increase in the number of erythrocytes in circulating blood, an increase in its hæmoglobin content, and a hæmo-concentration; and it is an established fact that this change is produced by the relative anoxia to which the subject is exposed and not to the fall of barometric pressure. Immature red corpuscles increase in number and the number of blood platelets is materially increased. Hurtado (1932) found that the viscosity of the blood was increased. He attributed this change to the increase of erythrocytes, for the serum viscosity was normal, but the relationship of the viscosity of serum to plasma was reversed. The increase of blood platelets produced by anoxia suggests that the coagulation time should be diminished and Hurtado observed a tendency to a short coagulation time at high altitudes.

In animals it is probable that the spleen is a source of the increased number of erythrocytes entering the blood stream at high altitudes. Schafer and Moore (1896) showed that anoxia caused the spleen to contract and Barcroft *et al* (1925) estimated that in

Leucocytosis commences soon after the beginning of anæsthetic administration. It reaches its greatest intensity in about four to eight hours, and may last for three to five days. Leake (1922) observed in rabbits, dogs and men that morphia in hypnotic dosage (gr. ¼ in man) produced a slight leucopænia and this was followed in about one hour by a leucocytosis lasting about twenty-four hours. The character of leucocystosis during nitrous oxide anæsthesia is midway between that of cyclopropane and local anæsthesia —and this suggests that leucocytosis during anæsthesia varies, not as the agent used, but as the level of anæsthetic depression produced.

Slight though definite changes occur in the erythrocyte content, the hæmoglobin content and the plasma volume of blood during natural sleep. These changes which take the form of a hæmodilution, have been attributed by Gollwitzer, Meier and Kroetz (1924) to the passage of fluids, poor in protein but rich in chloride and phosphorus, from the tissue spaces into circulating blood; the plasma volume of blood is consequently increased, with a relative fall in the number of erythrocytes and the hæmoglobin percentage.

It has been seen, when relative anoxia occurs, that the number of red blood corpuscles and the hæmoglobin content increase and a hæmo-concentration occurs. In Man, Webster (1929) with nitrous oxide and Waters and Schmidt (1934) and Taylor and Waters (1935) with cyclopropane, found no significant change in the blood concentration during anæsthesia with these agents, and Reeve (1946) states that no change in the blood concentration of Man occurred during nitrous oxide, ether or pentothal anæsthesia.

The observations of various workers are not in agreement regarding the action of particular anæsthetics on the blood concentration of given experimental animals. These results sometimes conflict, moreover, with those recorded for Man.

Drabkin and Edwards (1924) and Weiss (1926) observed no significant change in the blood concentration of cats and dogs during anæsthesia with iso-amyl barbiturate (amytal) and other barbiturates. Adolph and Gerbasi (1933) introduced 0·05 gm. of sodium amytal per kilo of body weight in a 10 per cent. solution and 2 0 gm. of urethane per kilo of body weight in a 10 per cent. solution,

cell membrane, for it has an oil/water partition coefficient of 1·89. Buckmaster and Gardner (1907) believed that chloroform combined with hæmoglobin in some way. McMechan (1926) states that spectroscopic examination of blood during acetylene, nitrous oxide and ethylene anæsthesia, disclosed no absorption bands; Rothmann (1888) and Killian and Mority (1931) reached the same conclusion with regard to nitrous oxide. Ulbrich (1888), Gangee (1896) and Manchot and Brandt (1909) are just as certain that nitrous oxide does combine with hæmoglobin, and Gangee stated that an absorption band could be observed in the violet part of the spectrum whose wavelength was 420·5 μ. Thus, the question of the combination of anæsthetics with hæmoglobin is undecided.

If a sufficient concentration is used, the common clinical anæsthetics act as hæmolytic agents *in vitro*.

Fuhner and Neubauer (1907) observed a general parallel between the hæmolytic and the anæsthetic concentration of various narcotics. The hæmolytic concentration is five to ten times that required to produce anæsthesia in tadpoles, and is greater than the anæsthetic concentration in mammals Hamburger and Ewing (1908) observed some hæmolysis during chloroform and ether anæsthesia in animals and Man, and they reported that hæmolysis is greater with chloroform than with ether; but Webster (1929) showed that hæmolysis is not produced by the concentrations of anæsthetics employed clinically in Man.

The leucocytosis that is produced by all forms of anæsthesia differs from that occurring when anoxia alone is present, for a differential count shows that the increase of white corpuscles during anæsthesia is due to a relative and an absolute increase in the polymorphonuclear neutrophils which are normal in size and character The source of these cells is not known but is probably red bone marrow, and neither splenectomy nor atropine prevents leucocytosis during anæsthesia. Leucocytosis is least during spinal and local anæsthesia and it is greatest during ether and cyclopropane anæsthesia. In spinal and local anæsthesia, leucocytosis reaches its greatest intensity about four to eight hours after the injection of these agents and returns to normal after about twenty-four to forty-eight hours During ether and cyclopropane anæsthesia, an increase of 200 per cent. to 300 per cent. of the normal white cell count may be reached during a long anæsthetic

in the blood concentration of animals during barbiturate anæsthesia, and he is of the opinion that extracellular fluids enter the blood stream and dilute the plasma proteins and corpuscles.

The evidence reviewed of the effect of barbiturate anæsthesia on blood concentration of dogs and cats is conflicting; but it seems that hæmo-dilution may occur during barbiturate anæsthesia and, when it does occur, hæmo-dilution may be attributed to the passage of corpuscles from circulating blood into the substance of a dilated spleen and/or to the passage of extracellular fluid from the tissue spaces into the blood stream.

Animal experiments show that hæmo-concentration occurs during ether anæsthesia. Mann (1916) observed a slight increase in the erythrocyte content of the blood of dogs and Boycott and Price Jones (1922) reported an increase of the erythrocyte and hæmoglobin content of the blood of rabbits during ether anæsthesia. Barbour and Bourne (1923) observed an increase of 16 per cent. of red corpuscles and a 10 per cent. increase of hæmoglobin in the blood of dogs during ether anæsthesia, and Searles and Essex (1936) observed an 18 per cent. increase of cell volume, a 15 per cent. increase of erythrocytes and a 19 per cent. increase of hæmoglobin in the blood of dogs during ether anæsthesia. McAllister (1937) found that the plasma volume of the blood of dogs was reduced on an average by 11·9 per cent. during ether anæsthesia. This change occurred within 15 - 30 minutes of the start of ether anæsthesia; plasma volume was not further diminished unless the depth of anæsthesia was increased and the blood concentration returned to normal within 2 - 3 hours of the termination of ether anæsthesia. McAllister concluded that the increased hæmocrit during ether anæsthesia in dogs was greater than could be accounted for by the fall of its plasma volume and Searles and Essex (1936) found that splenectomy reduced the hæmo-concentration of ether anæsthesia in dogs by about 50 per cent

Barcroft and Rothschild (1930) found that alcohol, ether and chloroform produced a contraction in the size of a dog's "exteriorized" spleen. Even the smell of a chloroform-ether mixture was sufficient to produce splenic contraction—which persisted throughout anæsthesia. During ether anæsthesia, the volume of the spleen was reduced to about one-half its resting

into the stomach of dogs and in each instance the results observed coincided with those of Drabkin and of Edwards and Weiss, for little alteration in the blood of these animals was observed. When the same doses of each anæsthetic was then injected intraperitoneally in dogs, hæmo-dilution was observed in the case of amytal and urethane produced hæmo-concentration. Adolph and Gerbasi considered that these results were due to the local action of each drug on the peritoneum. In the case of urethane, the method of administration is undoubtedly responsible for a loss of plasma volume with hæmo-concentration, for Wright (1943) states: "If urethane is painted on a capillary, little or no blood flows out at the venous end; capillary permeability is so increased that the entire plasma (including colloids) escapes into the tissue spaces." In respect to the barbiturates, it might be inferred that the blood gained fluids from the tissue spaces, as in natural sleep, and the result obtained after the intraperitoneal injection of barbiturates is in such contrast to those which follow their absorption from the stomach that it is probable, as Adolph and Gerbasi suggest, that the hæmo-dilution produced can be attributed to the method of their administration. Searles and Essex (1936), found however, that sodium amytal administered by mouth to dogs, produced a hæmo-dilution with a reduction of 19·7 per cent. in the number of erythrocytes, a reduction of 21 per cent. in the total cell volume and a reduction of 21 per cent. in the hæmoglobin concentration. Bourne, Bruger and Dreyer (1930) also reported hæmo-dilution with a fall of corpuscular volume of 5 - 10 per cent. one hour after amytal anæsthesia. They observed, moreover, a coincident increase in the volume of the spleen during phenobarbital anæsthesia and Cook and Rose (1930) found that the volume of the spleen increased during amytal anæsthesia in cats. Searles and Essex observed that the hæmo-dilution which occurs during barbiturate anæsthesia in dogs was completely abolished after splenectomy. This suggests that hæmo-dilution during barbiturate anæsthesia in these experimental animals may be due to the passage of corpuscles from circulating blood into the substance of a dilated spleen, and Adolph and Gerbasi (1933) found that the concentration of solids in the plasma of a dilated spleen was the same as that of circulating blood. Beecher (1940) states that changes in splenic volume cannot nearly account for the measured changes

physical stress is seldom present, splenic dilatation and hæmo-dilution occurs. This suggests that the presence or absence of stress during anæsthetic induction, rather than the specific anæsthetic employed, may be the factor responsible for alterations in splenic volume in dogs and cats during anæsthesia, and this conception may explain the discordant results which have been reported. The size of the human spleen relative to the body-weight, and the fact that splenic contraction or dilatation has not, to date, been observed in Man, makes it most improbable that the spleen materially influences Man's blood concentration during anæsthesia.

During the past ten years my surgical colleagues have frequently palpated the human spleen during surgical procedures at my request and they have not detected any alteration in the volume of the spleen during anæsthesia.

If hæmo-concentration with ether and hæmo-dilution with barbiturate anæsthesia do, in fact, occur in Man, it then seems probable that this alteration in blood concentration must be attributed to an alteration in the plasma volume of circulating blood. McAllister (1937) using the Gregersen technique with the dye T.1824 (Evans blue), calculated a decrease of 11·9 per cent. in the plasma volume of dogs during ether anæsthesia. Stewart (1937) measured the plasma volume of sixteen human subjects during ether anæsthesia using this same method and found an average reduction of plasma volume of 14 3 per cent, and an average increase of 7·5 per cent. in the volume of extracellular fluid. Reeve (1944) using Evans blue, however, found no significant change in plasma volume in Man during nitrous oxide, ether or barbiturate anæsthesia; and Gordon (1946-47) found no change of hæmocrit readings in curarized subjects during nitrous oxide-ether or cyclopropane anæsthesia.

The data concerning the effect of common clinical anæsthetics on the blood concentration in Man are inconclusive, and it is not possible to judge whether alterations in blood concentration are produced by the state of anæsthesia or by the action of the particular anæsthetic agent. During surgical procedures on anæsthetised subjects, however, occasional factors such as hæmorrhage, deficient venous return, shock, etc., may affect the blood concentration, but in clinical anæsthetic practice the issue is again confused.

volume, and these observers found that the greatest contraction occurred, not at the time of deepest anæsthesia but during the periods of greatest emotional and physical stress, i.e. during the non-cooperative stupor stage of induction and recovery. The de-nervated exteriorized spleen, on the contrary, showed little response to emotional stress during ether anæsthesia and the spleen was reduced to only about 70 per cent. of its resting volume at the period of deepest anæsthesia. Bhatia and Burn (1933) administered ether to a cat three hours after decebration and found that ether produced an immediate diminution of splenic volume and just as prompt an increase in its volume when the ether was withdrawn. When the sympathetic ganglia were paralysed with nicotine, ether produced no contraction in the spleen of the decebrate dog. Barcroft's work shows that splenic contraction occurs during ether and chloroform in dogs. It is due to emotional and physical stress during anæsthetic induction, and there is reason to believe that its intensity may be increased when, owing to hæmorrhage, surgical shock or deepening anæsthesia, the blood pressure of the animal falls below a certain critical pressure. The hæmo-concentration during ether and chloroform anæsthesia in dogs and cats may therefore be attributed to the passage of erythrocytes into circulating blood from the substance of the contracted spleen and/or to passage of plasma from circulating blood into the tissue spaces.

There is no reason to doubt that splenic contraction during ether and chloroform anæsthesia and splenic dilatation during barbiturate anæsthesia occurs in cats and dogs, and the size of the spleen and the sympathetic control which has been seen to exist is such in cats and dogs that its contraction or dilatation may exercise a material influence on their blood concentration. Barcroft's work demonstrates that sympathetic stimulation produces splenic contraction in these animals, and it is significant that splenic contraction with hæmo-concentration occurs in dogs and cats when ether or chloroform are employed—for with these agents induction is slow, and emotional and physical stress during this period is the rule rather than the exception. Nothing is known of the mechanism of splenic dilatation; but during natural sleep, which is approached in an essentially peaceful state of mind, and in barbiturate anæsthesia, in which induction is quiet and emotional and

the rate of clotting is likely to be normal, but nevertheless appears to be slow relative to the subject in whom rebreathing is practised.

The blood chemistry during anæsthesia has been reviewed in the previous section and it has been concluded that the changes which occur, vary, not as the particular anæsthetic used, but as the depth and duration of anæsthesia produced. The disturbance of blood chemistry during anæsthesia shows a certain similarity to that produced by anoxia.

Many observers have noted a rise in blood sugar during anoxia. This is attributed to glycogenolysis and it is less intense in starved animals. Gellhorn and Packer (1930) observed that anoxia produced an immediate rise of blood sugar which they attributed to the glycogenolytic action of adrenaline. They found that this glycogenolytic action was lost after long periods of relative anoxia (2 hours at 32 mm. of mercury of oxygen); this they presumed was not due to the depletion of liver glycogen.

Hurtado (1932) found no increase in the blood cholesterol of humans acclimatised at high altitudes, but Schmensky (1937) reported a rise in the blood cholesterol of men and dogs at an altitude of 5,000 feet. Hæmorrhage and exposure to a rarefied atmosphere produces a lipæmia in rabbits—generally agreed to be caused by an increase in plasma lipoids. Conclusions about the effects of oxygen lack on the blood lipoids of Man cannot be made, for rabbits do not respond like the other mammals studied.

Haldane *et al* (1919) and Henderson and Haggard (1920) observed that the hyperpnoea associated with relative anoxia produced an alkalosis in spite of a coincident depletion of the alkali reserve of the blood. The hyperventilation produced by relative anoxia lowers the tension of arterial carbon dioxide, the excretion of acid and ammonia by the kidneys is diminished and more base may be excreted, and the urine becomes alkaline. During the first hour of moderate anoxia, Peters and Van Slyke (1923) state that there is very little change in the alkali reserve of the body. Hyperpnoea causes a decrease in carbon dioxide tension and there is a slight rise of the blood pH.

In severe anoxia however, the alkalosis is replaced by acidosis which becomes more intense as death approaches. In severe anoxia the alkaline reserve soon begins to fall and Koehler *et al* (1925) found that the carbon dioxide combining power of the blood was

for such occasional factors are immediately treated with intravenous therapy.

Hurtado (1932) observed a tendency to a short coagulation time at high altitudes, and he suggested that this was due to the increased viscosity of the blood which occurs at high altitudes. When excess of carbon dioxide is added to relative anoxia, the blood clots very rapidly; and in clinical practice it is observed—and this is particularly noticeable during cyclopropane anæsthesia—that a few breaths of carbon dioxide materially increases the speed of clotting.

Sanford (1926) observed that, when nitrous oxide or ethylene was used during parturition, the coagulation time of the newborn was increased by 2 - 3 minutes, and Hamburger and Ewing (1908) found an increase in the coagulation time of dogs during nitrous oxide anæsthesia. Hamburger and Ewing (1908) in dogs and Rabinovich (1927) in Man, found that the coagulation time was diminished during ether anæsthesia. Straus and Rubin (1927) observed a reduction in the coagulation time in Man during ethylene anæsthesia, and Ellis and Barlow (1924) found that barbital decreases the coagulation time in cats. Variable results were obtained by Hamburger and Ewing (1908) of the effect of chloroform anæsthesia on clotting time, but in general there was slight decrease in the coagulation time. Taylor and Waters (1935) found no alteration in the coagulation time during cyclopropane anæsthesia.

These results are not in complete agreement one with another, and not wholly in accord with the effects observed in clinical anæsthetic practice. Thus, most anæsthetists and all surgeons would assert that bleeding from cut surfaces is greater and clotting is slower during cyclopropane than during nitrous oxide anæsthesia. This result is probably due to the high carbon dioxide content of inspired air during nitrous oxide anæsthesia while the reverse is true during cyclopropane anæsthesia. It is possible that the anæsthetic *per se* has little influence upon clotting time, and that the technique of administration may be the relevant factor. Thus, when the method of administration tends to produce excess of carbon dioxide and/or relative anoxia, the rate of clotting tends to be more rapid than normal, while in an adequately oxygenated subject anæsthetised with an efficient closed system of breathing,

and emotional stress during anæsthetic induction, that the variations in blood chemistry during anæsthesia conform to a general pattern, and that the intensity of these changes varies as the depth and duration of anæsthesia.

The Respiratory System. When Man or an experimental animal is exposed to complete oxygen lack or to overdose with anæsthetics which do not produce primary cardiac failure, breathing soon ceases and the character of the depression of the respiratory system is as follows: breathing first becomes shallow and this is followed by apneustic breathing, then by gasping breathing, then by a series of short gasps and, finally, respiratory movements cease and the volume of lung ventilation falls to zero. If the subject is successfully revived after respiratory failure of this kind, respiratory movement returns in the reverse order. Lumsden (1923) obtained the same sequence of respiration depression when the brain stem was sectioned at various levels. Hence, this characteristic sequence of respiratory failure can be attributed to the progressive depression of the several centres of respiratory integration in the brain; when at length the lowest medullary centre of respiratory integration is depressed by anoxia or by anæsthetic overdose, breathing ceases. The integrity of the respiratory system during anæsthesia therefore depends on adequate oxygenation throughout and on minute-to-minute control of the level of anæsthetic depression of the brain.

The maintenance of an adequate intracellular oxygen supply is determined by a sufficient partial pressure of oxygen in the atmosphere breathed and by the integrity of each and every link in the chain of events responsible for its carriage thence to the tissue cells of the body.

All anæsthetic gases and ethyl chloride can exert a partial pressure of 600 mm of mercury and more in an anæsthetic atmosphere at mean sea level; but the greatest partial pressure which the common clinical anæsthetic vapours exert (excepting ethyl chloride) is less than 600 mm of mercury unless their anæsthetic liquids are heated above room temperature. It follows that simple asphyxiation can readily be produced with anæsthetic gases, and with ethyl chloride; but with anæsthetic vapours, *except* ethyl chloride, simple asphyxiation is unlikely unless the anæsthetic liquid is heated. For obvious reasons, simple asphyxiation is unlikely to occur with

reduced to 9 8 volumes per cent. in the terminal stages of anoxic anoxia These observers found that severe anoxic anoxia can produce acidosis in the body with greater intensity and more rapidly than can any other condition. They were of the opinion that the production of acid in the cell began as soon as intracellular oxygen lack occurred, and that the effect of this was masked by the loss of carbon dioxide produced by hyperventilation in the early stages of anoxia. Henderson and Greenburg (1934) observed that an increase of blood lactic acid occurred only when the oxygen content of inspired air fell below 7 per cent. or 53 mm. of mercury. Henderson (1938) states that lactic acid appears in large amounts in blood only at the final stages of asphyxia when respiratory depression is present. The observations of many authorities indicate that the acidosis of severe anoxia cannot be accounted for solely by the accumulation of lactic acid; and Van Liere (1943) suggests that the blood concentration of other acids (such as acetone bodies and, in the light of recent work on muscle metabolism, of phosphoric. adenylic, glycerophosphoric and pyruvic acids) should be examined.

The evidence discussed indicates that the deleterious effect of oxygen lack is similar to the upset of blood chemistry produced during anæsthesia. Since anoxia is not controllable and because severe anoxia produces its action very rapidly, the synergism between anoxia and anæsthesia constitutes a very grave and material danger in clinical anæsthetic practice. Evidence has been discussed which indicates that in an adequately oxygenated subject the intensity of the blood changes produced during anæsthesia vary as the depth and duration of the level of anæsthetic depression The suggestion that, for a given level of anæsthetic depression, a particular anæsthetic agent produces more intense blood changes than its fellows—and/or blood changes outside the general pattern — is not substantiated when the common clinical anæsthetics are compared. The observations of the variation of blood concentration with different anæsthetics are conflicting and, moreover, evidence has been discussed which suggests that the presence or absence of emotional stress during anæsthetic induction is an important factor in determining variations from normal, not only in blood concentration but also in blood sugar, etc It can be concluded, in the absence of anoxia

in an edentulous subject; the tongue may be pressed or fall back to meet the palate and the posterior pharyngeal wall; a misplaced dental pack may obstruct nasal breathing if it lifts the soft palate or may completely obstruct if it passes downwards and backwards into the pharynx; vomitus or regurgitated stomach content may obstruct and may be aspirated into the pulmonary tract; foreign bodies such as dentures, teeth, tartar or regurgitated barium may lodge in any part of the respiratory tract and cause obstruction; blood and pus from the operation site may obstruct; pressure from without—such as that produced by a hæmorrhage into the substance of the tongue, by a quinsy or other inflammatory condition, by a large or substernal thyroid or by the pressure of a new growth—may obstruct breathing; finally, the potency of the trachea may have been reduced by pressure and/or by the softening or erosion of its supporting cartilages.

The inhalation of irritating gases and vapours, the presence of irritating foreign bodies in the respiratory tract, local stimulation of the naso-bucco-pharynx during light anæsthesia and certain types of intense proprioceptive stimulation during deep anæsthesia all produce reflex effects which result in respiratory obstruction of varying degrees. These reflex effects range from excessive salivary and bronchial secretions to spasm and/or oedema of the glottis or bronchospasm.

When emotional and physical stress is permitted to act during anæsthetic induction, the rhythm of breathing may be altered strikingly; salivation may be excessive; short periods of breath-holding may occur; or overbreathing may produce a carbon dioxide apnœa. Since hypnotics and atropine have been used as pre-anæsthetic medicants, emotional and reflex autonomic effects during anæsthetic induction have been reduced to minimal proportions. When, after adequate premedication, a rapid anæsthetic induction is achieved with non-irritants such as nitrous oxide, ethylene or intravenous barbiturates, then, in the absence of other factors, salivary and bronchial secretions are normal in volume—or are absent—and glottic spasm is the exception rather than the rule. In spite of such premedication and in the absence of other factors however, when mild stimulants—such as di-ethyl and di-vinyl ether, ethyl chloride, chloroform, cyclopropane or a high concentration of carbon dioxide—are inhaled, then salivary and bronchial

potent anæsthetic gases and with the potent anæsthetic vapour ethyl chloride; but with weak anæsthetic gases—such as nitrous oxide and *ethylene—simple asphyxiation is a real danger when* a greater depth of anæsthesia is demanded of these weak anæsthetics than is in their power to give.

In the presence of an adequate partial pressure of oxygen in the atmosphere to which the subject is exposed, shallow breathing and/or respiratory obstruction may prevent the mass movement of oxygen from this atmosphere to alveolar air sufficient to satisfy the subject's oxygen demands.

In normal conditions of life when the respiratory centre is functionally active, the volume of lung ventilation is proportional to the metabolic rate, and the volume of effective lung ventilation is sufficient to satisfy the oxygen demands of a subject breathing atmospheric air. Blood-borne anæsthesia, anæsthetic premedicants, surgical shock, and morphia and its allies as used in the post-operative period, frequently produce shallow breathing which is commonly attributed to depression of the respiratory centre. When the shallow breathing produced by narcotics and/or surgical shock, proves to be insufficient adequately to oxygenate the subject, it must be assumed that the respiratory centre is depressed; a compensatory increase in the oxygen partial pressure of inspired air must then be made and/or assisted respiration immediately instituted. When, however, adequate oxygenation is maintained in spite of shallow breathing, this diminished volume of lung ventilation is due to a lowered metabolic rate, and the respiratory centre is in fact regulating the volume of lung ventilation effectively and is not depressed. The volume of lung ventilation in a curarized subject with a functionally active respiratory centre may be insufficient to oxygenate adequately and it is not always realised that a like result may be produced during local and spinal anæsthesia In each *instance the oxygen content of* inspired air must be increased and/or assisted respiration must be instituted, in order to avoid depression of the respiratory centre by anoxia

Respiratory obstruction caused by mechanical or reflex effects produces asphyxia for it hinders not only the uptake of oxygen but also the excretion of carbon dioxide. Mechanical obstruction occurs from many causes The lips may fall together, especially

for in clinical anæsthetic practice, salivary and all other reflex secretions cease when the stage of complete sensory loss has been achieved, while in under-atropinized subjects, pilocarpine or prostigmine produces increased secretions at the level of complete sensory loss. This result can be attributed to the inability of the areas of sensory co-ordination of the brain to integrate the impulses from the periphery responsible for these secretions, and it indicates moreover that the concentration of blood-borne anæsthetics in arterial blood—and, in turn, in the glands themselves—is insufficient to depress the functional activity of the salivary glands at the level of complete sensory loss. Respiratory obstruction produced by excessive salivary secretions during anæsthetic induction is usually of a minor character.

Laryngeal spasm is recognised by the high-pitched " crowing " obstructive character of inspiration, and is due to a powerful adductor spasm of the vocal cords of varying intensity and duration. The effector side of the reflex arc which is responsible for this tonic adduction of the vocal cords, is the recurrent laryngeal nerve; its affector field which is very extensive, includes the true cords, the false cords, and all parts of the naso-bucco-pharynx. Indeed, stimulation of almost any part of the body may result in an adductor spasm of the vocal cords with consequent obstruction to breathing. In general, any stimulus which produces excessive salivation is also likely to be accompanied by spasm of the larynx; and, like excessive salivation, laryngeal spasm most commonly occurs during the non-cooperative stupor stage of anæsthetic induction and recovery. Rood and Webber (1930) state that they know of no case in which tracheotomy was necessary owing to the persistence of laryngeal spasm: if the stimulant producing it is withdrawn, the spasm will be relieved as soon as sufficient carbon dioxide has accumulated in arterial blood. In severe and prolonged laryngeal spasm, however, a relatively intense degree of anoxia may be produced before the spasm is relieved and, when at length inspiration does occur, the abduction of the vocal cords is feeble and relatively ineffective. On this account, it is of the utmost importance to ensure that the airway is unobstructed and the anæsthetic atmosphere contains adequate oxygen, so that the first inspiration after the spasm shall be effective in relieving this anoxia, for, in a subject whose cardiac reserve is impaired, a severe and

secretions may be excessive and glottic spasm of varying intensity may occur.

Saliva is the secretion of the parotid glands, the submaxillary glands, the sublingual glands and the small glands located in the deeper layers of the mucous membrane of the naso-bucco-pharynx. The parotid glands secrete a watery liquid which contains no mucin, the secretion of the submaxillary glands and that of the small glands of the mucous membrane is both serous and mucous, and the sublingual glands secrete a liquid which is rich in mucin. In normal conditions of life, mixed saliva consists of 99·4 per cent of water, 0·4 per cent. of mucin and 0·2 per cent. of inorganic solids, but there is little doubt that the constitution of mixed saliva varies within wide limits with emotional stimulus and the character of ingested food. Thus, intense odours produce excessive salivation, mild stimulants produce the copious secretion of serous saliva, and irritants and local trauma are apt to produce excess of stringy, tenacious saliva.

In the absence of other factors, Robbins (1935) found that in dogs, nitrous oxide, ethylene and the intravenous barbiturates were non-irritants and produced no increased secretion of saliva. During anæsthetic induction and in the absence of other factors, he found that di-ethyl ether produced a 550 per cent. increased secretion of saliva above normal, chloroform a 500 per cent. increased secretion and cyclopropane a 250 per cent. increased secretion above normal values. During surgical anæsthesia with all three anæsthetics, salivation ceased, but it increased again during anæsthetic recovery, by 400 per cent. in the case of di-ethyl ether and chloroform and by 350 per cent above the normal value in the case of cyclopropane This increased secretion may be attributed to reflex stimulation of the salivary glands through the sensory end-organs in the mucous membrane of the naso-bucco-pharynx, for Robbins observed no increased salivation when the cocainization of the mucous membrane inactivated these end-organs or when these irritating gases and vapours bypassed the mucous membrane of the larynx and the naso-bucco-pharynx. He observed that in dogs salivary secretions ceased during surgical anæsthesia, but the salivary glands themselves were functionally active, for an injection of pilocarpine produced an immediate copious flow of saliva at this level of anæsthetic depression. These results obtain in Man.

and glottic area is then sprayed with a 10 per cent. cocaine solution, and a rapid, trouble-free induction to the level of complete sensory loss is carried out with a non-irritant anæsthetic gas such as ethylene. It is unwise to use an airway or to pass an endotracheal tube in such a case, for the most trivial degree of trauma may precipitate the rapid onset of œdema—a calamity that must be foreseen and prepared against. A tracheotomy set must be ready for instant use and while it is impossible to pass a Magill's tube when œdema of the glottis is absolute, it should be remembered that a round-tipped, gum-elastic endotracheal catheter can be forced between the œdematous false cords without trauma, for the true cords are not affected in this condition. The passage of a gum-elastic catheter will allow adequate oxygenation to be maintained while an unhurried tracheotomy is performed. The passage of a Magill's tube when œdema of the glottis is anticipated or suspected must be judged a dangerous measure, for not only is it a source of irritation in such a subject, but it may also mask the onset of œdema of the false cords. Thus, a soldier with a deep-seated abscess of the neck was induced with nitrous oxide, oxygen and di-ethyl ether and was maintained through a Magill's tube with the same anæsthetic. Induction and maintenance was uneventful; when, after fifty minutes' anæsthesia, the anæsthetic ceased and the Magill's tube was withdrawn, the patient coughed. Respiratory obstruction, however, soon became apparent and he died within five minutes from asphyxia—which autopsy proved to have been caused by an absolute œdema of the false cords.

New growths of the pharynx or larynx may raise similar problems during anæsthesia, and are approached in the same way as for œdema of the glottis. An uncommon cause of laryngeal obstruction is the injury of one or both recurrent laryngeal nerves during surgical procedures

Finally, reflex effects can cause bronchial spasm or bronchospasm. Bronchial spasm may be produced by the presence of a foreign body in a bronchus and the bronchial constriction produced, together with the presence of the foreign body may result in deficient air entry and/or in the collapse of the lobe served by this bronchus Bronchospasm may be described as a tonic shortening and narrowing of the whole bronchial tree, and invariably results in anoxia of a degree which varies as the intensity and the duration

prolonged laryngeal spasm may produce a degree of anoxia sufficient to endanger the life of the subject. The danger of laryngeal spasm in cardiac subjects may be eliminated by spraying the pharynx and the larynx with a 10 per cent. solution of cocaine prior to anæsthetic induction.

When anæsthesia to the level of complete sensory loss has been achieved, laryngeal spasm generally ceases but Brewer *et al.* (1934) have shown in dogs—and all anæsthetists have observed in Man—that certain intense proprioceptive stimuli may produce adduction of the vocal cords during anæsthesia deeper than complete sensory loss. Thus, the forceful dilatation of the anal sphincter or traction on the peritoneum or the mesentery sometimes produces crowing inspiration and Brewer *et al.* observed that this effect is the result of adduction of the vocal cords produced by stimulation of the splanchnic nerves. This adduction of the vocal cords may persist for some time after the stimulus has ceased to act and it only gradually relaxes. It is a source of annoyance during surgical anæsthesia, but it seldom, if ever, causes anoxia.

Respiratory obstruction produced by œdema of the glottis is one of the most dangerous, and at the same time one of the most difficult problems with which the anæsthetist may be confronted. In this condition the true cords are seldom affected. The epiglottis is greatly swollen with œdema, the ary-epiglottic folds are swollen and œdematous and the œdema may involve the subglottic area. It is associated with trauma and with inflammatory conditions in the glottic area, such as laryngitis, cellulitis of the neck, erysipelas, diphtheria, etc , and with allergic conditions, with nephritis, and sometimes with the acute infectious fevers. The etiology of the condition warns the anæsthetist of the danger to be anticipated and it is important to realize that the most trivial degrees of local trauma during anæsthetic induction in such a subject may precipitate sudden intense œdema of the ary-epiglottic folds which then meet in the midline and completely obstruct the airway.

The only certain method of safely anæsthetising a subject in whom œdema of the glottis is either present or suspected is to perform a tracheotomy under local anæsthesia and then induce and maintain anæsthesia through this guaranteed airway. When, however, œdema of the glottis is only suspected or anticipated, tracheotomy may be judged too drastic a procedure; the pharynx

treatment of this condition. Atropine gr. 1/50 may also be administered intravenously, and takes at least 60 seconds to produce its peripheral effect.

The errors or accidents of anæsthetic induction and the pathological conditions of the subject described above are discussed in terms of the obstruction which they create to the entry of oxygen at an adequate pressure into the pulmonary system; but, even when there is free and full entry of an anæsthetic atmosphere containing oxygen at an adequate partial pressure into the lungs, the oxygen content of alveolar air may still fall below normal limits. Thus, emphysema increases the volume of functional residual air, and, when shallow breathing occurs in an emphysematous subject, anoxia may result. An open pneumothorax during anæsthesia may result in the collapse of the lung on the affected side, and will invariably cause some degree of under-oxygenation. In each instance, a high partial pressure of oxygen is necessary in the anæsthetic atmosphere, and assisted or controlled respiration at some degree of positive pressure may be desired or required. Again, when pulmonary secretions are excessive, they may produce some degree of obstruction in the respiratory passages, their accumulation may result in discrete or patchy atelectasis or in massive collapse, and their continued retention may result in pulmonary infection.

Pulmonary secretion is the product of glands which lie in the deeper layers of the respiratory epithelium and of goblet cells of the respiratory epithelium. In the trachea, glands are so extensive as to form an almost continuous layer and goblet cells are numerous. Both glands and goblet cells diminish progressively in number as the calibre of the broncial tree narrows, until at length when the bronchioles are reached both glands and goblet cells are absent. The glands normally secrete a watery liquid similar to that of the lacrimal glands; goblet cells secrete pure mucin. In normal conditions of life the combined secretion of the respiratory tract consists of 95 per cent. of water, 3 per cent. of mucin and 2 per cent. of solids. It serves to coat the inner surface of the respiratory passages with a moist, slightly viscid film. The respiratory epithelium of the finer bronchioles and air cells lacks cilia, glands and goblet cells—a fact suggesting that when bronchial drainage is efficient this part of the pulmonary

of the spasm. When there is severe bronchospasm, the larynx is closed, the bronchial tree is powerfully constricted, the thorax is fixed in the position of full expiration, and air entry into the lungs is difficult or impossible even when vigorous artificial insufflation is attempted. The afferent impulses responsible for this effect, like those which produce laryngeal spasm, may arise from the bronchial tract itself, from the naso-bucco-pharynx, the stomach, the uterus or in fact from almost any part of the body; the resulting efferent *para-sympathetic impulses are carried to the constrictor muscles* of the bronchial tree in the fibres of the vagus nerve. Histamine is also known to produce intense bronchospasm.

Bronchospasm usually occurs in response to trivial stimulation —or without any obvious cause—during the stage of anæsthetic sleep (Guedel's first plane of anæsthesia), when the sympathetic entities of the *hypothalamus are depressed* and the para-sympathetic entities of this basal nucleus are still functionally active. No reference has been discovered which describes broncho-spasm during deep anæsthesia and it has been observed that bronchospasm is relieved as anæsthesia deepens to and beyond the level of complete sensory loss It is significant that bronchospasm has been recognised as a *rare* complication of anæsthesia only since the introduction of curarine as an anæsthetic adjuvant. It is still more significant when curarine is used as an anæsthetic adjuvant that bronchospasm does not occur in adequately atropinized *subjects when anæsthesia is carried to and maintained at the level* of complete sensory or deeper It may occur, however, when dangerously light anæsthesia is maintained, *i.e.* when anæsthetic maintenance is lighter than the level of complete sensory loss. The meagre evidence that is available suggests that bronchospasm is a para-sympathetic reflex effect associated with the stage of anæs-thetic sleep; nothing constructive can be said of the rôle of histamine in the production of bronchospasm during clinical anæsthetic practice It can be avoided by adequate atropinisation and a swift, trouble-free induction to the level of complete sensory loss *Treatment, when it does occur, consists* of the use of all the means at one's disposal to prevent anoxia and to deepen anæsthesia; the passage of a gum-elastic catheter followed by the forceful insufflation of an anæsthetic atmosphere with a high oxygen content appears to give the best hope of the successful

subsequent shortening and narrowing of the bronchial tree varies as the depth of breathing, it follows that not only the volume of the " battering ram " of air expelled, but also the intensity of the shortening and narrowing of the whole bronchial tree—the effectiveness of the cough in fact—depends upon the depth of the inspiration which precedes the violent expiratory effort.

Van Allen *et al* (1930) have shown that a lobular collateral air circulation exists in the lungs. They found that when the permeability of the interlobular septa is normal the blocking of a finer bronchiole by a plug of viscid mucus does not result in the collapse of the lobule which its serves, if alveolar air contains its normal partial pressure of nitrogen; for the obstructed lobule can be efficiently aerated by diffusion through this septa from unobstructed adjacent lobules. They observed moreover, that it is difficult, if not impossible, to block a finer bronchiole with a plug of viscid mucus if an effective cough was present, for the lobular collateral air circulation allows the act of coughing to reach the air cells of obstructed lobules. The increased intrapulmonary pressure generated by an effective cough thus hastens the diffusion of gases from the unobstructed to the obstructed lobule; it moreover builds up a higher pressure of alveolar air in the obstructed lobule, so that with the next violent expiratory act of coughing the bronchiolar plug is the more readily dislodged. The effect of a cough is generally held to be confined to the upper respiratory passages, but it is clear that it exerts a powerful effect throughout the whole pulmonary system.

The normal defence of the pulmonary system is considerably embarrassed or is completely disorganised during all forms of anæsthesia. Thus, breathing is shallow in all forms of anæsthesia; the cough reflex is abolished during blood-borne anæsthesia to the level of sensory loss and deeper, and its effectiveness is curtailed in varying degrees during local or spinal anæsthesia; ciliary action is abolished during blood-borne anæsthesia and is inhibited in varying degrees by the premedication used prior to local or spinal anæsthesia; finally, the nitrogen content of alveolar air and in turn that of the whole body is excreted throughout anæsthetic administration when a semi-closed method is employed. For these several reasons sterile or infected secretions

system, although moist, is mucous-free. In view of the evaporation produced by the continuous rhythmic flow of air over this surface, the amount of pulmonary secretion required is considerable. Some idea of its volume is afforded by the fact that about 330 grammes of water are excreted daily from the pulmonary system

In normal conditions of life the pulmonary system is defended against air-borne infection by the presence of this moist, slightly viscid film of pulmonary secretion and by its movement towards the exterior under the combined effects of ciliary action and the rhythmic expansion and contraction of the whole respiratory tract during breathing. The cilia of the respiratory tract extend as far as the small bronchioles, and bacteria and small particles of foreign matter entangled in the film of respiratory secretion are propelled by ciliary action towards the exterior at a rate equivalent to 40 - 60 inches per hour. Ciliary action is assisted by the lengthening and widening of the whole bronchial tree on inspiration and by its shortening and narrowing on expiration; and the effectiveness of bronchial drainage varies in an upward and a downward direction with the depth of breathing. The efficiency of bronchial drainage in normal conditions of life is indicated by the fact that alveolar air is invariably sterile even in the presence of naso-pharyngeal infection.

When the volume and/or the viscosity of pulmonary secretion increases above normal limits, this mechanism is incapable of maintaining efficient bronchial drainage, and secretions tend to gravitate to and accumulate in the finer bronchioles and air cells. In this event, two further means of protecting the pulmonary system are called into action They are the act of coughing—a temporary expedient to deal with this state of emergency—and the presence of the lobular collateral air circulation—a means of neutralizing the effect of the obstruction of the finer bronchioles by excessive and/or viscid secretion

A cough consists of an inspiration followed by an explosive expiratory act requiring the active co-operation of the larynx and all the muscles of expiration. Since residual air is a fixed volume which cannot be expelled by any muscular effort, the volume of air expelled by the violent expiratory act of coughing depends upon the volume of air drawn into the lungs by the previous inspiration. Since, moreover, the degree of lengthening and widening and the

of salivary and bronchial glands. It can be inferred, moreover, that the local irritation of the mucous membrane of the respiratory tract, which results in the production of mucus-secreting goblet cells, is of a minor character even with di-ethyl ether, for local irritation with the production of mucus-secreting goblet cells could be expected to continue and even increase as the concentration of di-ethyl ether increased with deepening anæsthesia: this in fact does not occur. Thus, in a Boyle-Davis gag anæsthetic for tonsillectomy, when concentrated di-ethyl ether impinges on the palate during expiration, it is observed that the palate is *dry* during deep surgical anæsthesia but that, as anæsthesia lightens, and coincident with the return of the pharyngeal reflexes, discrete beads of secretion appear on the palate: their presence is itself interpreted as a sign of lightening anæsthesia. This effect implies that palatal glands do not secrete, that goblet cells are not present in significant numbers during deep di-ethyl ether anæsthesia, and that these glands begin to secrete as soon as the subject can react in a reflex manner to external stimulation. It can be concluded that even with di-ethyl ether (the most irritating inhalation anæsthetic in common clinical use) that excessive salivary and bronchial secretion results mainly from reflex glandular stimulation, that local irritation of the mucous membrane is not a significant factor, and that in the absence of infection the mucin content of these secretions is not abnormally high. Since excessive salivary and bronchial secretions during anæsthesia are the result of reflex stimulation, they can be prevented or greatly reduced by the cocainization of the naso-bucco-pharyngeal mucous membrane prior to anæsthetic induction, and by adequate premedication preceding a swift and trouble-free induction to the level of complete sensory loss.

When these secretions are sterile their accumulation in the pulmonary system early in anæsthetic maintenance is of little moment, for their high water-content and low mucin-content permits rapid evaporation, and neither atelectasis nor infection is to be anticipated.

A very different result can be expected after an anæsthetic administered to a subject with an infection of the nose or nasal sinuses, the mouth, the pharynx or the larynx, for infected material secreted at these sites during anæsthetic induction may readily enter the pulmonary system from above during anæsthetic maintenance.

from the naso-bucco-pharynx may freely enter and accumulate in the respiratory system during anæsthesia.

No experimental evidence of the behaviour of pulmonary secretions during anæsthesia is available. It is known that irritation and/or sepsis of the bronchial epithelium produces a rapid increase in the number of goblet cells, and Engel and Newns (1941) state that every columnar cell of the bronchial mucous-membrane is capable of becoming a goblet cell which secretes pure mucin. The mucous content of the glandular secretion increases when glands are irritated, and infected glands secrete muco-pus. Hence, in pathological conditions of the respiratory passages, goblet cells increase in number, glands become mucus-secreting, and the volume and viscosity of these secretions increase significantly in the trachea and the large bronchi where most glands and goblet cells are located.

It might, therefore, be assumed that when irritating anæsthetic gases or vapours are inhaled glands become mucus-secreting and that goblet cells significantly increase in number. In this instance, the volume and the mucin content of bronchial secretions would materially increase in the trachea and in the large bronchi where most glands and goblet cells are located; and this would apply particularly to water-soluble irritants such as di-ethyl ether.

When respiratory infection is absent, di-ethyl ether produces a large volume of salivary and bronchial secretion in under-atropinized subjects during the non-cooperative stupor stage of anæsthetic induction, and even in adequately atropinized subjects, the volume of salivary and bronchial secretion is still greater than normal. In either event, however, when anæsthesia to the level of complete sensory loss has been achieved, salivary and bronchial secretions cease, and it is observed as anæsthetic maintenance proceeds that the bubbling produced by the presence of these secretions gradually ablates and the respiratory tract becomes dry. This effect can be attributed to the arrest of glandular secretions when the subject ceases to react in a reflex manner to external stimulus and to the subsequent evaporation—by the rhythmic flow of air produced by lung ventilation—of the water-content of secretions present in the respiratory tract That these secretions do dry up is the indication of a high water-content and a low mucin-content, they are mainly the product of the reflex stimulation

bronchial drainage; for any given posture during anæsthesia, the site of focal drainage will be recognised as the common site of the atelectasis and/or the pneumonitis which sometimes follows the administration of an anæsthetic.

In the absence of an effective cough—and this condition obtains during clinical anæsthesia—the gravitation of viscid secretion into the finer bronchioles is likely to produce obstruction to air entry into the corresponding lobule of the lung. If, in these circumstances, the interlobular septa is rendered impermeable to the passage of gases, either by the coating of this surface by viscid secretions or by the œdema of irritation or infection, the lobular collateral air circulation fails and there may be a patch of collapse corresponding in area to the size of the obstructed lobule. The probability of the collapse of this lobule is considerably enhanced by any factor which accelerates the absorption of its contained gases into blood flowing in the pulmonary capillaries. The two common factors which hasten gaseous absorption from obstructed air cells during anæsthesia are: (1) the excretion of the nitrogen-content of alveolar air produced when a semi-closed system of breathing is employed; and (2) the diminished circulatory rate through the pulmonary capillaries produced by cardiac failure, diminished venous return or surgical shock.

Coryllos and Birnbaum (1928) observed in dogs when a main bronchus was obstructed or ligated that the gas content of the corresponding lobe was completely absorbed into circulating blood and the lobe collapsed to the consistency of liver, in 30 - 36 hours. When, however, the nitrogen-content of alveolar air was reduced to small proportions by the exposure of the dog to an oxygen atmosphere containing no nitrogen for 30 - 60 minutes before bronchial ligation, the absorption of the gas-content of the obstructed lobe was accelerated, and it collapsed to the consistency of liver in 20 - 30 minutes.

In Man, dry alveolar air contains 80 per cent. of nitrogen at a partial pressure of 583 mm. of mercury. Molecular nitrogen, a non-reactive substance, is not utilized in body metabolic processes, and in normal conditions of life it is in gaseous equilibrium with everything round about it, viz. with the nitrogen-content of atmospheric air, with the nitrogen dissolved in circulating blood, in the tissue cells, and in the tissue fluids of the whole body. Hence, the

When infection of the pulmonary system itself is present prior to anæsthesia then the complete breakdown of the mechanism of bronchial drainage during anæsthetic maintenance ensures the retention and accumulation of these infected secretions—which are rich in mucin and may even consist of muco-pus. Despite the fact that goblet cells increase in number when inflammation is present at any of these sites, salivary and bronchial glands are the main source of infected viscid secretions during anæsthesia. Even when they are infected, the reflex secretion of these glands may be greatly reduced by cocainization of the naso-bucco-pharynx and by adequate premedication followed by a swift and trouble-free induction to the level of complete sensory loss. When, with deepening anæsthesia, the secretion of these glands is arrested, goblet cells may continue to secrete pure mucin; and although goblet cell secretion is unlikely materially to increase the volume, it may significantly increase the viscosity of retained pulmonary secretions during anæsthetic maintenance. Hence, the most important single result of the administration of an anæsthetic to a subject with pre-existing naso-bucco-pharyngeal and/or respiratory infection, is the retention of infected viscid secretions in the pulmonary system during anæsthetic maintenance. It is clear that this is the result of the embarrassment or complete disorganisation of the defences of the pulmonary system which occurs during blood-borne anæsthesia and during local anæsthesia affecting the trunk muscles, irrespective of the technique of administration.

Brock (1947) has shown that when pulmonary drainage is ineffective the posture of the subject is mainly responsible for the character of the movement of retained secretions in the pulmonary system. When the subject is supine, as in most surgical procedures, the first lung segment to be filled with retained secretions is the apical segment of the lower lobes; then follow the posterior branches of the bronchi of the upper lobes or the remaining posterior bronchi of the lower lobes. On the assumption of the sitting position, the basal segments are the site of focal drainage; and when the subject lies on his side, the lateral divisions of the anterior and posterior bronchi of the upper lobe of the dependent lung are first filled with excess of retained secretion. Brock presents conclusive evidence that when pulmonary stasis is present the posture of the subject determines the character of

Like nitrogen, helium is a non-reactive gas which is not utilized by the body. It must be realized that helium, like nitrogen, becomes effective as an air-cell scaffold only when the body is fully saturated with helium at an adequate partial pressure and when the helium content of the anæsthetic atmosphere, of alveolar air, of circulating blood and of the tissue cells and tissue fluids, are in gaseous equilibrium; for it is only so that it remains immobile in alveolar air. Since the rate of diffusion of helium is more than twice that of nitrogen, this state of gaseous equilibrium is rapidly assumed; but, on the other hand, should conditions be favourable, helium is just as rapidly absorbed from an obstructed lobule into circulating blood—and such favourable conditions must eventually be created when anæsthesia ceases. There is little doubt that the slower diffusion-rate of nitrogen, with the fact that nitrogen is a normal constituent of atmospheric air, together make this gas the ideal air-cell scaffold—which is retained *in situ* when open or efficient closed systems of breathing are employed for anæsthetic administration. When respiratory obstruction is present, the addition of helium to the anæsthetic atmosphere enables this atmosphere to pass more readily through the narrowed air passages and may permit adequate oxygenation to be maintained until the cause of the obstruction is removed.

The tendency to atelectasis following the loss of the nitrogen air-cell scaffold during anæsthesia with a semi-closed system of breathing may be countered in another way. Thus, if the respiratory and anæsthetic gas-and-vapour content of alveolar air is always materially greater than the mass of these gases and vapours which can dissolve in blood flowing in the pulmonary capillaries in the time available for gaseous exchange between these two systems, then the gases and vapours lost by alveolar air to circulating blood per unit time will not significantly reduce the mass of these gases and vapours in alveolar air, which will, in this event, constitute an effective air-cell scaffold. This set of circumstances can be created and maintained only if the anæsthetic is administered at some degree of positive pressure. It is the writer's belief that the pressure of the anæsthetic in the reservoir of a semi-closed system of breathing at the end of inspiration should never fall below a positive pressure of about 2 mm. of mercury. In clinical anæsthetic practice, however, it is a common event to

nitrogen-content of alveolar air is not metabolised and, being in gaseous equilibrium, it cannot move. It therefore constitutes an inert scaffold which maintains the air cells patent. Even when the oxygen, the carbon dioxide and the water-vapour content of alveolar air have been absorbed, the nitrogen air-cell scaffold remains and, because it is absorbed very slowly, effectively retards the rate of onset of atelectasis.

Boycott *et al* (1908) estimated that at mean sea level the whole body of a man weighing 70 kilos contained about one litre of molecular nitrogen in solution. When such a man is exposed to an oxygen atmosphere containing no nitrogen, 50 per cent. of the nitrogen-content of his body is excreted in about ten minutes and he excretes the whole of his nitrogen-content in about one hour.

When the subject inhales an air-anæsthetic mixture, or when an efficient closed system of breathing is employed, the nitrogen-content of the body is not significantly reduced during anæsthesia and the nitrogen air-cell scaffold remains to effectively protect from threatened atelectasis. When a semi-closed system of breathing is employed for anæsthetic administration, the nitrogen-content of the whole body is excreted in about one hour and the protection afforded by the nitrogen air-cell scaffold is lost. Thus, when a semi-closed system of breathing (*e g* a Boyle's apparatus) is used for the administration of nitrous oxide, oxygen and di-ethyl ether, the subject inhales this anæsthetic atmosphere at each inspiration, but at each expiration exhales nitrous oxide, oxygen, di-ethyl ether, carbon dioxide, water vapour and nitrogen The nitrogen content of his body and of alveolar air will consequently be reduced by 50 per cent. after about ten minutes' anæsthesia and it will have fallen to zero when anæsthesia has lasted about 60 - 70 minutes. Hence, during anæsthesia administered with a semi-closed system of breathing, atelectasis is more likely to follow the retention of viscid secretion in the finer bronchioles than when an open or closed system of breathing is employed; for when alveolar air contains little or no nitrogen, the absorption of respiratory and anæsthetic gases and vapours in unstable gaseous equilibrium, from alveolar air into circulating blood, is considerably accelerated and atelectasis is the more likely to occur.

It has recently been suggested that protection from atelectasis is afforded by the addition of helium to the anæsthetic atmosphere.

impaired; and in a subject breathing air the tension of oxygen in blood leaving the pulmonary capillaries is normal—but blood circulates more slowly through the tissues. The impaired circulatory rate not only increases the time available for gaseous exchange between blood and tissues but also causes carbon-dioxide accumulation, which facilitates the dissociation of oxyhæmoglobin. In consequence of this, the amount of oxygen received by some tissues is excessive while in others it is inadequate, venous blood returns to the pulmonary capillaries with a lower oxygen tension than normal, and the uptake of oxygen from alveolar air is accelerated. This set of circumstances was termed by Van Slyke, "stagnant anoxia." When stagnant anoxia is present, the slow rate of blood-flow through the pulmonary capillaries increases the time available for gaseous exchange between this blood and the gases and vapours of alveolar air. This is a favourable condition for the rapid absorption of respiratory and anæsthetic gases and vapours from an obstructed lobule, lobe or lung into circulating blood. When the nitrogen-content of alveolar air has been depleted, the respiratory and anæsthetic gases and vapours in unstable gaseous equilibrium are absorbed from an obstructed lobule, lobe or lung even more rapidly when stagnant anoxia slows the rate of blood-flow through the pulmonary capillaries.

Two further pulmonary conditions which may develop during anæsthesia are associated with the diminished velocity of pulmonary blood flow produced by stagnant anoxia. They are bi-lateral massive collapse of the lungs and acute pulmonary œdema.

In the two cases of bi-lateral massive collapse with which the author is conversant, death occurred on the operating table within twenty minutes of the commencement of the anæsthetic. In each instance, nitrous oxide, oxygen and di-ethyl ether was administered with a Boyle's apparatus; neither respiratory obstruction nor bronchospasm was present throughout, but breathing was shallow, for both subjects were in a pre-uræmic state with a blood urea of over 200 mgs. per cent. Full oxygenation was readily attained, but the subject did not bleed freely when the skin incision was made. In spite of full oxygenation elsewhere, cyanosis of the lobe and the helix of the ears soon developed, and this phenomenon —which the author interprets as a sign of severe stagnant anoxia—

see the bag of a Boyle's machine collapsed to half its total volume at the end of inspiration, and this creates a set of circumstances which, in the absence of the nitrogen air-cell scaffold, predisposes to atelectasis.

When finer bronchioles are blocked with viscid secretion, the lobular collateral air circulation provides an alternative method of aerating obstructed lobules, and this mechanism is an important means of protection from threatened atelectasis. There is no alternative method of aerating lung units larger than lobules, and, when a bronchus or the main bronchus of a lung is obstructed, air entry into the corresponding lobe or lung is completely arrested unless and until the obstructing plug or foreign body is removed by posture and coughing, or by surgical interference. The obstruction of the air passages at a level higher than the bronchioles is therefore a serious event. In the absence of the nitrogen air-cell scaffold it may produce massive collapse of the lung before measures can be taken to remove the obstruction Even when a semi-closed system of breathing is employed, respiratory obstruction produced by the errors or accidents of anæsthetic induction, (glottic spasm, broncho-spasm, etc.) *are unlikely to be followed by atelectasis, for the* obstruction is likely to be of a transient nature; and at this period of anæsthesia the nitrogen-content of alveolar air is not materially *depleted. When such a respiratory obstruction* occurs late in anæsthetic maintenance, or early in the post-anæsthetic period after prolonged anæsthesia with a semi-closed system of breathing, the absence of the nitrogen air-cell scaffold makes atelectasis a real possibility, which is increased by the presence of stagnant anoxia. The obstruction produced by viscid secretions in the larger air passages is determined by the posture of the subject and unless the volume of accumulated secretion is excessive, it is likely to be of a local nature, confined to the site of focal drainage. When the nitrogen-content of alveolar air is normal, the complete collapse of the lobe or of the whole lung can be expected within about 30 hours unless the mucous plug is removed. In the absence of a normal nitrogen-content in alveolar air, the onset of collapse is hastened and will be further accelerated when this set of circumstances occurs in a subject with stagnant anoxia.

When cardiac output is diminished by cardiac failure, diminished venous return or surgical shock, the circulatory rate is

Finally, Waters (1942) warns of the effect of excessive suction, which is capable of causing bilateral massive collapse of the lungs.

Local inflammation of the respiratory epithelium from infection or by irritation from the entrance of anæsthetic liquids or noxious gases such as chlorine or phosgene into the pulmonary system may each result in local œdema of the respiratory mucous membrane with the exudation of excess of fluid into the air cells. Pulmonary œdema may also occur in subjects with pathological conditions of the cardio-vascular system (*e g* arterial hypertension and coronary or aortic disease) which predispose to left ventricular failure.

The œdema produced by irritants is likely to be of a local nature, and fluid extravasates from the pulmonary capillaries into the interlobular septa, thence into the alveolar spaces, where it coagulates and fills the air cells with fibrin. As a result, the uptake of oxygen by and the excretion of carbon dioxide from blood flowing in the pulmonary capillaries is seriously hindered. The velocity of blood-flow through the pulmonary capillaries is also diminished, and venous congestion of the lungs occurs.

Unlike that produced by local irritation, the œdema produced by cardiac effects is of a general nature affecting the whole of both lungs. It is associated with pulmonary congestion and with a diminished velocity of pulmonary blood-flow. The principle factor in its causation is left ventricular failure. When acute pulmonary œdema occurs during anæsthesia, its onset is sudden. Huge volumes of fluid suddenly accumulate in the lungs; and, if the subject is placed in the Trendelenburg position, fluid may gravitate out of the pulmonary system in a steady stream. Acute pulmonary œdema is most likely during anæsthesia in a subject with stagnant anoxia, because of the characteristic diminished velocity of pulmonary blood-flow. Its onset may be precipitated by the pulmonary congestion produced by coughing or glottic spasm. In such a subject these predisposing causes may be eliminated by spraying the nasopharynx and larynx with a 10 per cent. solution of cocaine before anæsthetic induction. It is thought that the high negative intrapleural pressure produced by the powerful inspiratory efforts necessary to overcome respiratory obstruction (caused, for example, by a too small or kinked endotracheal tube) may also cause the extravasation of fluid into the air cells.

has consistently proved to be a reliable indication of venous congestion produced by a dangerously slow circulatory rate. Breathing became progressively shallower but responded to the exhibition of carbon dioxide only for a short time; at length respiration had to be assisted; assisted respiration in turn became difficult; and finally it was impossible to insufflate the lungs by manual pressure on the bag of the Boyle's apparatus, and the subject died about twenty minutes after anæsthesia had been begun. At the autopsy both lungs were seen to have collapsed to the size of an orange and were airless. There was no evidence of a pneumothorax nor of respiratory obstruction produced by a foreign body or a mucous plug.

In both these cases, microscopic examination of sections of the lungs revealed nothing more than atelectasis. The excretion of nitrogen throughout and the slow circulatory rate through the pulmonary capillaries were undoubtedly relevant factors in these fatalities, but the complete absorption of the entire contents of alveolar air so rapidly in the absence of respiratory obstruction and pneumothorax suggests that there were some additional factors. The only other factor common to both cases was shallow breathing produced by the action of accumulated poisons on the respiratory centre, for both subjects were in a pre-uræmic state.

One can only speculate on the cause of this catastrophe in the hope of suggesting a possible remedy. Keith (1909) suggests that shallow breathing produces uneven ventilation of the lungs, which expand on inspiration like a Japanese fan. With the slow rate of pulmonary blood flow and the loss of nitrogen air-cell scaffold, it is possible that the absorptive capacity of blood flowing through the least ventilated parts of the lung might well exceed their gas-and-vapour content and they would soon collapse. Then, as breathing became shallower, this effect would be produced in the next least ventilated part of the lung and so on. In the two cases cited, this suggests that assisted respiration commenced earlier in anæsthesia might well have saved the situation; but nowadays, when shallow breathing and a dangerously slow circulatory rate are present, it is usual to retain the nitrogen content of alveolar air by the use of a closed system of breathing, to maintain an effective cardiac output by the use of intravenous therapy, and to employ assisted or controlled respiration at an adequate positive pressure.

Finally, Waters (1942) warns of the effect of excessive suction, which is capable of causing bilateral massive collapse of the lungs.

Local inflammation of the respiratory epithelium from infection or by irritation from the entrance of anæsthetic liquids or noxious gases such as chlorine or phosgene into the pulmonary system may each result in local œdema of the respiratory mucous membrane with the exudation of excess of fluid into the air cells. Pulmonary œdema may also occur in subjects with pathological conditions of the cardio-vascular system (*e.g.* arterial hypertension and coronary or aortic disease) which predispose to left ventricular failure.

The œdema produced by irritants is likely to be of a local nature, and fluid extravasates from the pulmonary capillaries into the interlobular septa, thence into the alveolar spaces, where it coagulates and fills the air cells with fibrin. As a result, the uptake of oxygen by and the excretion of carbon dioxide from blood flowing in the pulmonary capillaries is seriously hindered. The velocity of blood-flow through the pulmonary capillaries is also diminished, and venous congestion of the lungs occurs.

Unlike that produced by local irritation, the œdema produced by cardiac effects is of a general nature affecting the whole of both lungs. It is associated with pulmonary congestion and with a diminished velocity of pulmonary blood-flow. The principle factor in its causation is left ventricular failure. When acute pulmonary œdema occurs during anæsthesia, its onset is sudden. Huge volumes of fluid suddenly accumulate in the lungs; and, if the subject is placed in the Trendelenburg position, fluid may gravitate out of the pulmonary system in a steady stream. Acute pulmonary œdema is most likely during anæsthesia in a subject with stagnant anoxia, because of the characteristic diminished velocity of pulmonary blood-flow. Its onset may be precipitated by the pulmonary congestion produced by coughing or glottic spasm. In such a subject these predisposing causes may be eliminated by spraying the nasopharynx and larynx with a 10 per cent. solution of cocaine before anæsthetic induction. It is thought that the high negative intrapleural pressure produced by the powerful inspiratory efforts necessary to overcome respiratory obstruction (caused, for example, by a too small or kinked endotracheal tube) may also cause the extravasation of fluid into the air cells.

Histamine may be a causative factor, and it is known that excess of intravenous fluid—particularly saline—may result in pulmonary œdema. Since pulmonary œdema is probably the penultimate event in total cardiac failure, suggestions regarding its treatment during anæsthesia are scanty and of a general character. The predisposing cause of its onset must be eliminated immediately. Venesection may assist, for it reduces venous pressure and, in turn, pulmonary congestion. The assumption of the Trendelenburg position with oxygen insufflation through a patent airway probably offers the best chance of the subject's survival, and he should be adequately morphinized during anæsthetic recovery.

If, however, the errors and accidents of anæsthetic administration discussed above have been successfully avoided, and if the volume of lung ventilation is adequate and the entry of an anæsthetic atmosphere containing adequate oxygen into the air cells is free and unobstructed, then the partial pressure of oxygen in alveolar air during anæsthesia will be maintained within the normal limit of 100 mm. of mercury. In the absence of excess of fluid in the air cells or of œdema of the respiratory membrane, the velocity of diffusion of oxygen and carbon dioxide through this membrane is such that blood leaves the pulmonary capillaries saturated to 95 per cent. of its carrying capacity and containing oxygen at a tension of 90 mm. of mercury and carbon dioxide at a tension of 40 mm. of mercury. When however, the total blood volume, or its hæmoglobin, is depleted by accidents such as hæmorrhage, or by disease such as anæmia, or when the circulatory rate is slower than normal, as for example when stagnant anoxia is present, then the subject may suffer from oxygen lack. Hæmorrhage or anæmia should be corrected by the intravenous administration of whole blood before anæsthesia and these effects are neutralized during anæsthetic maintenance by the intravenous transfusion of whole blood and by the increase in the oxygen-carrying capacity of circulating blood produced by an increase in the partial pressure of oxygen in the anæsthetic atmosphere. Finally, when congenital abnormalities of the cardiovascular system are present (*e g* congenital pulmonary stenosis), the volume of pulmonary blood flow may be reduced to such a degree that efficient oxygenation of the subject is impossible.

Even when the intracellular oxygen demands of the subject

are satisfied and anæsthesia is below the level necessary to depress the functional activity of the respiratory centre, breathing may be inhibited or completely arrested in a number of ways.

Carbon dioxide acts directly on the respiratory centre and stimulates the respiratory centre reflexly through the chemoreceptors of the arch of the aorta and the carotid body. An increase in the carbon-dioxide content of inspired air stimulates the respiratory centre during anæsthesia, and breathing becomes at first deeper and then more rapid. When excess of carbon dioxide is washed out of alveolar air by overbreathing, or by too vigorous assisted respiration, the tension of carbon dioxide in arterial blood reaching the respiratory centre falls· a carbon dioxide apnœa occurs and lasts until the tension of carbon dioxide in arterial blood builds up again to the threshold value necessary to stimulate the respiratory centre.

The distention of the lungs acting through the stretch receptors in the lung substance produces a prolonged expiratory effort, and, if excessive positive pressure is used in the anæsthetic atmosphere and distention is sufficiently forceful, breathing ceases in the position of full inspiration. In like manner, moderate suction produces a strong inspiratory effort; if excessive suction is employed, breathing ceases with the chest in the position of full expiration. The chemical regulation of the respiratory centre by carbon dioxide determines the extent to which the lungs must expand or collapse before this reflex comes into play and it is for this reason that controlled respiration can be instituted most readily if a carbon dioxide apnœa is produced, with, at the same time, some degree of positive pressure in the anæsthetic atmosphere. No deleterious effects have ever been observed during controlled respiration; on the contrary, it confers material benefits. It can be inferred that the production of a carbon dioxide apnœa is a harmless procedure if at the same time the intracellular oxygen demands of the subject are satisfied. The opinion has been advanced in the above discussion, moreover, that a measure of positive pressure in the anæsthetic atmosphere is of material benefit.

Excessive positive pressure in the anæsthetic atmosphere nevertheless introduces very dangerous effects. As a result of experiments on the fatal effect of excessive intrapulmonary pressure carried out during an investigation of submarine escape accidents,

Polack and Adams (1932) found that as soon as the intrapulmonary positive pressure exceeds 80 mm. of mercury, traumatic air embolism occurs. There is stretching and tearing of many alveoli and their contained capillaries; air is forced into these vessels and passes into the right heart, where it is broken up into fine bubbles which fill the heart with foam. This arrests the circulation, and the subject dies from anoxia. Quite apart from the danger of traumatic embolism, these observers found that an intrapulmonary positive pressure of 80 mm. of mercury sustained for 10 seconds produced grave embarrassment of the circulatory system. Thus, the circulation of blood through the lungs was so reduced that the venous pressure rose to 120 mm. of water, and the diminished venous return to the right heart so reduced the cardiac output that the systolic arterial pressure fell from 156 to 28 mm. of mercury. Within one minute of the release of the positive intrapulmonary pressure, however, the systolic arterial pressure rose to 128 mm of mercury. In thoracic surgery, a positive pressure of 30 to 40 mm of mercury is often employed for short periods of time to inflate a collapsed lung just before the surgeon restores the continuity of the chest wall. This can occasion no harm to the lungs and, provided the duration is short, can produce only a transient embarrassment of the cardiovascular system.

Incomplete respiratory obstruction produces fatigue of the respiratory centres and, if it continues for a sufficient period of time, will eventually cause the complete depression of the respiratory centre.

Moore and Binger (1927) observed that obstruction to *inspiration* produced rapid breathing, a diminution in the tidal air volume, and a marked reduction in the minute volume of lung ventilation which was associated with anoxia and acidosis. Obstruction to *expiration* slowed the rate of breathing and produced a constant decrease in the minute volume of lung ventilation; but anoxia and acidosis was less than that produced by inspiratory obstruction. In clinical practice, all anæsthetists have observed the very great contrast in the character of breathing and the rate of onset of respiratory fatigue produced on the one hand by a given degree of obstruction to expiration and on the other to the same degree of obstruction to inspiration. Thus, when a semi-closed system of breathing is employed, an adequately oxygenated subject

will expire against the resistance of the expiratory valve for two hours and more without depression of the respiratory centre. Again, in a closed system of breathing, if the soda-line canister is placed in the expiratory phase, the resistance it occasions does not produce fatigue of the respiratory centre. When, however, the canister and/or an ether vapourizer is placed in the inspiratory phase of a closed circuit, then breathing is often jerky and laboured, and is soon followed by fatigue of the respiratory centre. Respiratory fatigue of this origin can be eliminated, and an asthenic subject can be saved the effort of breathing, if controlled respiration is used in a closed system. In this instance, the anæsthetic atmosphere is insufflated into the lungs by manual pressure on the anæsthetic reservoir at a rate and at a tidal air volume chosen by the anæsthetist. Expiration is entirely passive and is produced by the decrease in the size of the thoracic cage by virtue of its own weight, the elastic recoil of the costal cartilages, and the elasticity of the lungs which always tend to return to a certain mean position.

There is little doubt that resistance or incomplete obstruction to expiration produces effects that are insignificant compared with the same degree of resistance or obstruction during inspiration; and in each instance these effects are due primarily to the intensity of anoxia produced.

The danger of oxygen poisoning during anæsthesia has occasionally been mooted, but oxygen at a partial pressure of 456 mm. of mercury (60 per cent.) can be breathed for an indefinite time with perfect safety and oxygen at atmospheric pressure (760 mm of mercury) can be breathed for four hours and more without ill effect.

The data discussed shows that the functional activity of the pulmonary system is modified during anæsthesia, and the deviations from normal which occur fall naturally into two heads. Anoxia of varying duration and intensity may occur, and pulmonary stasis of varying degrees is invariably produced, during anæsthesia. Adequate oxygenation is essential to the safety of the subject. Pulmonary stasis seldom endangers life during anæsthesia but is the first step in the chain of events which may lead to a pulmonary complication in the post-operative period.

Pulmonary stasis invariably occurs during surgical anæsthesia, for pulmonary drainage is ineffective or is abolished during the whole period of surgical anæsthesia. Thus, during local or spinal anæsthesia on the trunk, breathing is shallow and the cough is ineffective; and during blood-borne anæsthesia breathing is shallow and the cough reflex is abolished. In these conditions, secretions tend to gravitate to and accumulate in the site of focal drainage of the pulmonary system. Hence, irrespective of the means employed to produce surgical anæsthesia, pulmonary drainage is ineffective or is completely abolished during the whole period of anæsthesia. Pulmonary stasis is therefore the natural corollary of the state of surgical anæsthesia. It bears no relation to the anæsthetic employed but only to the level of anæsthetic depression produced, and is the only constant and inevitable factor acting during surgical anæsthesia which predisposes to a pulmonary complication in the post-anæsthetic period. In this discussion, it will be referred to as the inevitable factor. Table 55, taken from the work of King (1933), illustrates the fact that post-operative pulmonary complications which can be attributed primarily to this inevitable factor occurred with all the forms of anæsthesia in common clinical use; and, as might well be expected, anæsthetists who have had experience of continuous intravenous barbiturate anæsthesia have found that the pulmonary stasis produced during this form of anæsthesia similarly predisposes to pulmonary complications in the post-anæsthetic period.

TABLE 55.

INCIDENCE OF PULMONARY COMPLICATIONS AFTER DIFFERENT TYPES OF ANÆSTHESIA. (KING, 1933.)

Type of Anæsthetic	Pulmonary Complications (%)
Di-ethyl ether	12 4
Di-ethyl ether & Spinal	18·3
Spinal	16 7
Local	18 4

In a series of 7,065 cases examined by King (1933), 629 (8·9 per cent) developed a pulmonary complication in the post-anæsthetic period and it is clear in 91 per cent. of cases that the

inevitable factor, pulmonary stasis, was *per se* insufficient to produce a post-operative pulmonary complication. Many occasional factors may act in conjunction with pulmonary stasis to precipitate a post-operative pulmonary complication; they divide naturally into two groups—(*a*) those which act during anæsthesia and (*b*) those which act in the post-anæsthetic period.

TABLE 56.

THE INCIDENCE OF POST-OPERATIVE PULMONARY COMPLICATIONS AFTER PENTOTHAL, NITROUS OXIDE, OXYGEN AND DI-ETHYL ETHER.

Site of Operation	No pre-operative respiratory infection			Minor respiratory infection in pre-operative period		
	No.	Post-operative Pulmonary Complication	%	No.	Post-operative Pulmonary Complication	%
Extra-abdominal	130	—	0	74	1	1·3
Abdominal	22	1	4	19	8	42 0
Total operations	152	1	0·65	95	9	9 7

Any factor increasing the volume and/or the viscosity of the secretions which may enter and accumulate in the pulmonary system during anæsthesia predisposes to atelectasis: if this retained secretion is infected, bronchitis or pneumonitis may occur. During induction with inhalation anæsthetics, reflex salivary and respiratory secretions are significantly increased in a healthy subject by local stimuli caused, for instance, by the too early insertion of an airway or endotracheal tube, by irritating inhalation anæsthetics, by anoxia, and by the emotional and physical stress of prolonged troublesome induction. When naso-pharyngeal or respiratory infection is present before anæsthesia, such reflex secretions are excessive and they are infected. In an adequately premedicated subject, whether healthy or infected, these reflex secretions may be greatly reduced or even entirely abolished (1) if the naso-bucco-pharynx is sprayed with a 10 per cent. solution of cocaine before anæsthesia or (2) if induction is swift and trouble-free to the level

Pulmonary stasis invariably occurs during surgical anæsthesia, for pulmonary drainage is ineffective or is abolished during the whole period of surgical anæsthesia. Thus, during local or spinal anæsthesia on the trunk, breathing is shallow and the cough is ineffective; and during blood-borne anæsthesia breathing is shallow and the cough reflex is abolished. In these conditions, secretions tend to gravitate to and accumulate in the site of focal drainage of

TABLE 55.

INCIDENCE OF PULMONARY COMPLICATIONS AFTER DIFFERENT TYPES OF ANÆSTHESIA. (KING, 1933.)

Type of Anæsthetic	Pulmonary Complications (%)
Di-ethyl ether	12·4
Di-ethyl ether & Spinal	18 3
Spinal	16 7
Local	18·4

the pulmonary system. Hence, irrespective of the means employed to produce surgical anæsthesia, pulmonary drainage is ineffective or is completely abolished during the whole period of anæsthesia. Pulmonary stasis is therefore the natural corollary of the state of surgical anæsthesia. It bears no relation to the anæsthetic employed but only to the level of anæsthetic depression produced, and is the only constant and inevitable factor acting during surgical anæsthesia which predisposes to a pulmonary complication in the post-anæsthetic period. In this discussion, it will be referred to as the inevitable factor. Table 55, taken from the work of King (1933), illustrates the fact that post-operative pulmonary complications which can be attributed primarily to this inevitable factor occurred with all the forms of anæsthesia in common clinical use; and, as might well be expected, anæsthetists who have had experience of continuous intravenous barbiturate anæsthesia have found that the pulmonary stasis produced during this form of anæsthesia similarly predisposes to pulmonary complications in the post-anæsthetic period

In a series of 7,065 cases examined by King (1933), 629 (8·9 per cent.) developed a pulmonary complication in the post-anæsthetic period and it is clear in 91 per cent. of cases that the

secretion, and nothing the anæsthetist can do will diminish the volume or viscosity of the residual secretion. Successful surgical interference in such cases is assured only by certain positive measures which the anæsthetist must take. It is essential that this residual secretion shall not be further increased by reflex secretions: adequate premedication, cocainization of the naso-pharynx, followed by a swift and trouble-free induction to the level of complete sensory loss, will minimize or entirely abolish this danger. Suction must be employed throughout anæsthesia to prevent the accumulation of this residual secretion, and its spread to healthy segments of the lungs must be blocked by posture and the use of a correctly placed cuffed endotracheal tube.

It is reasonable to assume that an irritant inhalation anæsthetic increases the possibility of a post-operative pulmonary complication. There is an ingrained belief that in this respect di-ethyl ether is the chief offender, despite the contrary statistical evidence that the administration of a spinal or a local anæsthetic on the trunk does not lead to a diminution in the incidence of post-operative pulmonary complications. Table 55 showed that in King's series di-ethyl ether had in fact the lowest incidence of pulmonary complications. An irritating inhalation anæsthetic may pre-dispose to a post-operative pulmonary complication in two ways, namely, by increasing the volume and/or the viscosity of pulmonary secretions, and by decreasing the permeability of the interlobular membrane. The volume of reflex secretions depends upon the effectiveness of premedication and the time taken to arrest these secretions by the attainment of anæsthesia to the level of complete sensory loss. Their viscosity depends upon whether or not the relevant glands are infected. It is often suggested that di-ethyl ether predisposes to atelectasis by increasing the viscosity of these secretions, but in uninfected subjects their rapid evaporation during surgical anæsthesia indicates their high water and low mucin content. It is significant, too, that the administration of di-ethyl ether to an asthmatic subject earns his gratitude, for he is invariably freer from symptoms in the post-anæsthetic period than heretofore. There is little to substantiate the view that di-ethyl ether significantly increases the viscosity of retained secretions in uninfected subjects; but the volume of infected viscid secretion may be reflexly increased when there is infection. In each instance, the volume

of complete sensory loss—for, at this level of anæsthetic depression, reflex secretions cease. The reflex secretions which occur during anæsthetic induction are of little consequence providing they are not infected—for, if anæsthesia is maintained at the level of complete sensory loss or deeper, reflex secretion is arrested and any secretion which may have accumulated in the pulmonary system soon evaporates. This conclusion is reflected in Table 56, where it can be seen that of 152 subjects whose chests were normal prior to anæsthesia, only one (0·65 per cent.) developed a pulmonary complication—a mild bronchitis—in the post-anæsthetic period. Reflex secretions which are infected contain a greater proportion of mucin and their bacterial content is high. Consequently, the evaporation of the water-content of such secretions during surgical anæsthesia tends to leave plugs of infected tenacious mucous in the respiratory passages. Atelectasis and infection are therefore likely to follow a prolonged and troublesome induction in infected subjects, and the likelihood is enhanced if a semi-closed system of breathing is used and the nitrogen air-cell scaffold is lost during anæsthesia Table 56 shows that when respiratory infection is present prior to anæsthesia, post-operative pulmonary complications are about 15 times more frequent than in healthy subjects.

When anæsthesia to the level of complete sensory loss has been achieved reflex secretions cease, but there are two occasional factors which may increase the volume of retained pulmonary secretions during anæsthetic maintenance. If the level of depression is allowed to become lighter than complete sensory loss, reflex secretions re-commence, and when anæsthesia is maintained throughout at the level of complete sensory loss or deeper, cardio-vascular distress may produce acute pulmonary œdema. In each instance, this retained secretion may interfere with adequate oxygenation during anæsthetic maintenance and it predisposes to atelectasis and/or infection in the post-anæsthetic period.

Finally, the volume and viscosity of the secretions which occur with certain gross pathological conditions of the lungs is such that the normal mechanism is incapable of promoting efficient bronchial drainage in the pre-anæsthetic period. In these subjects, called "wet lung cases," excess of infected tenacious secretion is present in the lungs before anæsthesia. The state of anæsthesia will further accentuate the accumulation of this type of retained

assessed at all accurately is the infective factor during inhalation anæsthesia. In 1941 hospital beds were in such demand that about one-third of the subjects submitted to surgical interference had a pre-existing naso-pharyngeal or minor respiratory infection: the data of Table 56 were obtained during this period. It is seen that subjects with a pre-existing infection of a minor character developed a post-operative pulmonary complication about fifteen times more frequently than did healthy subjects; but this occasional factor was not, however, a decisive one, for 90 per cent. of the infected subjects did not show exacerbation of their pre-existing infection nor did they develop pulmonary complication in the post-anæsthetic period. These figures indicate that pulmonary stasis and these several occasional factors are not always decisive in producing a post-operative pulmonary complication, and it may be inferred that there are factors which may act with sufficient intensity in the post-operative period to precipitate a pulmonary complication.

Clinical observation shows that a post-operative pulmonary complication is usually established within 24 - 36 hours of the cessation of anæsthesia. Graham (1923), who observed a number of subjects with bronchial fistula, states: " When a patient with a bronchial fistula develops an acute infection of the nasal sinuses, the mucous membrane of the exposed bronchus becomes red and swollen and discharges large quantities of secretion which is at first almost pure mucus, but which later becomes muco-purulent. Local manifestations of acute infection in the exposed bronchus usually do not appear until about 24 hours after the onset of the acute sinus infection and bacterial examination of the secretion from the nasal sinuses and the exposed bronchus almost always reveals the same organism."

When an otherwise healthy subject suffers from coryza or a minor respiratory infection, there is little doubt that secretions accumulate in the finer bronchioles during natural sleep; but there is seldom any pulmonary catastrophe, for atelectasis and/or infection of the lung parenchyma is prevented by the removal of these retained infected secretions immediately on awakening by the combined result of an efficient collateral air circulation and an effective cough. This suggests that protection from a post-operative pulmonary complication would be achieved if an efficient

of reflex secretion can be greatly reduced or entirely abolished if premedication is adequate and if a balanced combination of anæsthetics is used to carry anæsthesia swiftly to the level of complete sensory loss. Thus, Beecher and Adams (1942), reviewing a five-year series of 260 di-ethyl ether and oxygen anæsthetics, administered in a closed system of breathing for major thoracic surgical procedures in subjects with pulmonary tuberculosis, concluded that di-ethyl ether can be used safely in the presence of pulmonary tuberculosis without aggravating this disease. This result implies that reflex secretion can be minimized or abolished, and that di-ethyl ether in the concentration used in clinical anæsthesia does not irritate the interlobular membrane.

It now remains to compare inhalation anæsthesia with spinal and local anæsthesia on the trunk—when irritation of the interlobular membrane cannot be held to occur.

The intensity and duration of the pulmonary stasis during spinal anæsthesia and local anæsthesia on the trunk varies as the height of anæsthesia and the character of the local anæsthetic used. Local irritation of the pulmonary tract is absent, but emotional stress may increase the volume of reflex secretion in inadequately premedicated subjects. The paralysis of vasoconstrictors in spinal anterior nerve roots predisposes certain subjects to cardiovascular distress, which may produce anoxia and/or circulatory effects and so increase the volume of retained secretions. The combination of pulmonary stasis with these occasional factors predisposes to a pulmonary complication in the post-anæsthetic period. The data compiled by Sise (1932) from the figures of Brunn and Brill (1930), Foss and Kupp (1930), Johnson (1931) and Thompson (1931), show that the incidence of post-operative pulmonary complications in these series (1) after spinal and (2) after inhalation anæsthesia was as 2·6 : 2·7. Hence, the incidence of pulmonary complication in the post-anæsthetic period is of the same order in both forms of anæsthesia. Irritation of the pulmonary tract during a correctly administered inhalation anæsthetic is therefore to be considered an insignificant factor.

It can be concluded that each of these several occasional factors react with the pulmonary stasis which inevitably occurs during anæsthesia to predispose to a pulmonary complication in the post-anæsthetic period The only occasional factor which can be

operations it is usually only 30 - 35 per cent. of the pre-operative level. The ability to breathe deeply, to cough effectively, and to successfully expel retained secretions in the immediate post-operative period is therefore curtailed after abdominal operations; moreover, the efficiency of this protective mechanism is progressively reduced as the site of abdominal operation moves from the pubis towards the costal margin. It follows that a pulmonary complication should occur more frequently after abdominal than after extra-abdominal operations and that the incidence of post-operative pulmonary complications should increase as the site of abdominal operation approaches more closely to the costal margin. Table 57 shows that this is so.

TABLE 57.

THE INFLUENCE OF THE SITE OF OPERATION ON THE INCIDENCE OF POST-OPERATIVE PULMONARY COMPLICATIONS.

Site of Operation	Post-operative Pulmonary Complications		
	King (1933)		Harris (1941)
	In Women %	In Men %	In Men %
Stomach and duodenum	17	47	35
Gall bladder	14	36	28
Intestine	13	26	24
Appendix	6	14	25
Hernia	4	9	14
Gynæcological	6	—	—
Miscellaneous abdominal	5	11	20
Total—Abdominal	8	18	20
Total—Extra-abdominal	0 8	1·04	0.7

(*Note* D S King's figures refer to civilians, T A B Harris's figures to soldiers, one-third with pre-existing respiratory infection.)

Table 57 also shows that for any given intra-abdominal operation post-operative pulmonary complications are about twice as frequent in men as in women. This can be attributed to their respiratory habits.

collateral air circulation was present in the immediate post-anæsthetic period and if retained secretions were removed with the same effectiveness as after natural sleep within 12 - 24 hours of the cessation of anæsthesia.

After extra-abdominal operations, excluding only thoracotomies, the subject regains the ability to breathe deeply and cough effectively as soon as anæsthetic recovery is complete. Because the thoracic musculature is intact and the abdominal muscles have not been traumatised, the subject can breathe deeply without pain and his vital capacity is undiminished. Because he can breathe deeply, he can cough effectively and successfully expel retained secretions early in the post-anæsthetic period. His ability to protect his chest is therefore similar to that after natural sleep, and in the absence of other factors a pulmonary complication after such extra-abdominal operations should be rare. In clinical anæsthetic practice—irrespective of the type of anæsthetic used—it is generally agreed that the incidence of pulmonary complications after extra-abdominal operations, excluding only thoracotomies, is in the region of 1 per cent. in both sexes. Disappointment is sometimes expressed that modern methods of anæsthesia have not completely eliminated pulmonary complications after such extra-abdominal operations, but is is clear that the virulence of a pre-existing infection must always play a dominant rôle. When the permeability of the inter-lobular septa is diminished by inflammation, discrete, patchy atelectasis may occur, particularly if in addition the nitrogen air cell scaffold has been lost during anæsthetic maintenance. Since the incidence of pulmonary complications after such extra-abdominal operations is much the same order after inhalation anæsthesia and after spinal and local anæsthesia on the trunk, it is unlikely that inhalation anæsthetics in the concentrations used in clinical practice can in fact irritate the inter-lobular septa; but a virulent pre-existing infection and the loss of the nitrogen air cell scaffold are important factors which predispose to a post-operative pulmonary complication.

After abdominal operations, however, because of the trauma which has been inflicted on the abdominal muscles, breathing is painful and is consequently restrained and shallow. Carlson (1923) states that the vital capacity of the subject after lower abdominal operations is reduced by 50 per cent., and after upper abdominal

tight binder and by the supine position; it may be increased in the post-operative period by Fowler's position, by rational dressings and by the relief of abdominal distention with oxygen therapy, the application of heat to the abdomen, and the appropriate use of a Ryle or Miller-Abbott tube or a rectal tube. The most important single measure capable of ensuring the early return of the ability to inspire and cough effectively is the relief of pain on inspiration; this is achieved by the use of adequate morphia in the post-anæsthetic period. In wet lung cases, in which the expulsion of retained secretions early in the post-anæsthetic period is essential to the success of surgical interference, morphia is to be used freely, but with discrimination. Thus, after a thoracoplasty, morphia gr. 1/4 every 6 hours, is used as a routine for the first forty-eight hours; and despite a very painful operation site coupled with a wet lung, the subject coughs effectively and in effect saves his life. These measures are combined with free movement in bed, massage and supervised breathing exercises.

The value of supervised breathing exercises is sometimes queried on the ground that the prophylactic effect of the hyperventilation produced in the post-anæsthetic period by carbon dioxide has proved disappointing. Thus, King (1933) treated alternate cases with carbon dioxide in the post-anæsthetic period for one year and then compared the results of this measure in 648 treated and 667 untreated cases. He found that the hyperventilation produced by carbon dioxide did not reduce the incidence of post-operative pulmonary complications, which was 4·1 per cent. in treated and 4·0 per cent. in untreated cases. Tattersall (1941) appears to contradict this result, for in a military hospital in which about 40 per cent. of cases had a pre-existing respiratory infection, he reduced the incidence of post-operative pulmonary complications from 79 per cent. to 53 per cent. by the use of carbon dioxide in the post-operative period. When, however, the incidence of post-operative pulmonary complications is very high, any favourable factor is likely to produce a significant result. When, for example, warm di-ethyl ether from a Shipway's apparatus was substituted for open ether, Geoffrey Marshall (1923) stated that the incidence of post-operative pulmonary complications immediately fell from 54 per cent. to 14·7 per cent. Hyperventilation, *per se*, can be regarded only as a favourable factor, but it is important to

Men generally are diaphragmatic breathers, and this type of breathing is almost invariably present in middle-aged men with rigid costal cartilages whose chests are relatively fixed. On inspiration their abdominal muscles contract, and after an abdominal operation a deep inspiration must inevitably cause *considerable pain. After abdominal section, shallow breathing* and, in consequence, an ineffective pain producing cough is the rule in males. This predisposes to the retention of accumulated secretions and so to a post-operative pulmonary complication. Women, on the contrary, are generally costal breathers—or else they readily adopt this type of breathing in the post-operative period. On inspiration their abdominal muscles relax; after an abdominal operation, a deep inspiration may be made without appreciable pain. Thus, of thirteen females observed after cholecystectomy, only one required morphia in the post-operative period. Hence, women can inspire deeply enough without pain to produce an effective cough in the post-operative period. The retention of accumulated secretion is therefore less likely to occur in women than in men and when subjected to any given type of abdominal operation *they are less likely to develop a pulmonary* complication in the post-operative period. The object of supervised breathing exercises in the post-operative period is to develop costal breathing and by the relief of pain on inspiration, to encourage a productive cough.

There is little doubt that the return of the normal mechanism of pulmonary drainage early in the post-operative period may abort a potential post-operative complication while the longer secretions are retained in the pulmonary system in the post-operative period, the more likely is a major complication to become established. The factors acting to delay the early return of efficient pulmonary drainage in the post-anæsthetic period may be discussed in terms of those factors which *inhibit* deep breathing and those which render the subject *incapable of making the effort* of deep breathing.

The most important single factor responsible for the subject's inability to breathe deeply and cough effectively in the post-anæsthetic period is pain on inspiration. Its intensity is determined mainly by the site of surgical interference, but it may be accentuated by the presence of drainage tubes The vital capacity of the subject may also be reduced by abdominal distention, by a too

of anæsthesia, to anoxia during anæsthetic maintenance and in the post-anæsthetic period, and to the cardiovascular effects produced during deep, prolonged anæsthesia.

Even when the greatest measure of anæsthetic protection is afforded, it is generally agreed that certain types of surgical procedures (for example, the removal of a hollow viscus, such as the stomach or the bladder) produce excessive exhaustion and lowered vitality in the post-operative period.

It is also agreed that deep, prolonged anæsthesia produces excessive exhaustion and lowered vitality in the post-anæsthetic period. This can be attributed to the degree of ketosis produced during anæsthesia, and this ketosis is intensified by anoxia during anæsthetic maintenance or in the post-anæsthetic period. It is diminished if anoxia is avoided throughout and is greatly reduced by the lightest and shortest anæsthetic consistent with safety and an efficient anæsthetic preparation. With an efficient anæsthetic preparation for a given major intra-abdominal surgical procedure, the degree of ketosis is greatest when a blood-borne anæsthetic is used; it is reduced in intensity when spinal or local anæsthesia is employed. When blood-borne anæsthesia to the level of complete sensory loss is used with d-tubo-curarine chloride to produce muscular relaxation, a safe and efficient anæsthetic preparation is achieved, with, at the same time, a very significant reduction in the intensity of ketosis. This is reflected in the sense of well-being and striking lack of apathy and exhaustion after major intra-abdominal surgical interference when blood-borne anæsthesia to this level of depression is combined with d-tubo-curarine chloride. Moreover, this reduction in the intensity of ketosis has materially widened the field of surgical interference; for procedures which may last for from 3 - 7 hours and were regarded as impossibilities in the pre-curare era, are now commonplace.

Prolonged major surgical procedures of this kind have revealed another potent source of a lowered vitality and exhaustion in the post-operative period. When intense prolonged muscular relaxation is produced with blood-borne or local anæsthetics or with d-tubo-curarine chloride, it is observed that cardiovascular distress invariably occurs after a period of time which varies from subject to subject. This can be attributed to a progressive reduction of cardiac output produced when shallow breathing and complete loss

remember that the deep breathing produced by carbon dioxide, in the absence of appropriate morphia, may cause considerable pain which in turn defeats the intention of making possible an effective cough.

Factors may also be present in the post-operative period that render an adequately morphinised pain-free subject unwilling or incapable of making the effort necessary to breathe deeply and cough effectively, and this predisposes to a post-operative pulmonary complication.

There are rare subjects who lack the moral stamina to help themselves and also those who actively resent any form of treatment. These subjects are prone to post-operative pulmonary complications.

It is difficult for obese subjects and those with emphysema, poor chest expansion and flabby musculature to breathe deeply and cough effectively in normal conditions of life; after intra-abdominal operations this difficulty is even greater. In these subjects intelligent nursing in the post-operative period, coupled with supervised breathing exercises and the willing co-operation of the subject himself, are of real value

Apathy and a lowered vitality often prevents an effective cough in the post-operative period. This state may be due to pre-existing medical and surgical conditions such as anæmia, cardiovascular disease, the cachexia of advanced malignant disease, diffuse peritonitis and other intense toxæmias or to post-operative surgical complications such as abdominal distention, obstruction, paralysis ileus, and to toxæmias, uræmia, etc. Appropriate medical and surgical treatment of these several conditions is essential, and should be combined with efficient nursing and appropriate physiotherapeutic treatment in the post-operative period.

When these several predisposing factors are absent, the apathy, lowered vitality and exhaustion which may occur in the post-operative period is usually described as post-operative and/or post-anæsthetic shock Shock is a generic term which gives little information of the factors acting to produce it. This apathy, lowered vitality and exhaustion in the post-operative period may be attributed to the trauma, produced by the nature of the surgical interference, to the ketosis produced by the depth and duration

When these measures are combined with the return of efficient pulmonary drainage early in the post-anæsthetic period, post-operative pulmonary complications after extra-abdominal operations are reduced to negligible proportions; but after intra-abdominal operations their effect may be completely neutralized in the post-operative period by pulmonary stasis produced by diminished vital capacity and pain on inspiration. Methods of permitting the subject to breathe deeply and cough effectively, based on the relief of pain and increased vital capacity, have been discussed; if this can be accomplished within the first 24 - 36 hours of the cessation of anæsthesia, the incidence of post-operative pulmonary complications after intra-abdominal operations is materially reduced. Thus, in a military hospital where about one-third of the cases had a pre-existing infection and where post-operative treatment was to all intent and purpose non-existent, the incidence of post-operative pulmonary complications was 78 per cent.: in another military hospital working under similar conditions, using the same type of anæsthesia, and doing similar surgery on the same type of subjects, active post-operative treatment on the lines discussed reduced the incidence of post-operative pulmonary complications and/or an exacerbation of the pre-existing infection to 7.5 per cent.

This, in turn, suggests that, except in wet lung cases, the errors and accidents of induction and maintenance can be largely neutralized if the subject can be made to breath deeply and cough effectively early in the post-anæsthetic period. The only factor which may prevent or defeat post-anæsthetic treatment is the apathy, lowered vitality and exhaustion of the subject in the post-anæsthetic period. If pre-anæsthetic preparation has been thorough and anoxia and cardiovascular distress are avoided throughout, the lightest anæsthetic consistent with safety and an efficient anæsthetic preparation offer the greatest guarantee of an active, mentally alert subject in the post-anæsthetic period. Cardiovascular distress during anæsthesia and in the post-anæsthetic period not only endangers life, but also produces exhaustion and a diminished vital capacity in the post-operative period. It therefore favours the retention of secretions in the post-operative period and moreover, such subjects often fail to respond to antibiotic drugs. Apart from all else, cardiovascular distress in the post-anæsthetic period favours

of muscle tone in skeletal muscles at length reduce the venous return to the right heart below a certain critically low level. This vicious circle is the result of diminished venous return and is immediately reversed if whole blood is given intravenously at a proper rate. If cardiovascular distress of this origin is ignored, or if it is not swiftly corrected, the subject may die during anæsthesia; if he does return to the ward, he will suffer from cardiovascular distress in the post-anæsthetic period, with the lowered vitality and exhaustion which accompanies cardiac failure. Apart from all else this post-anæsthetic exhaustion, coupled with a diminished circulatory rate, predisposes to pulmonary complications which in the aged are frequently fatal.

The data discussed indicate that the side-actions of the individual anæsthetics in common clinical use play no part, or at best a minor rôle, in the production of a post-operative pulmonary complication. Post-operative pulmonary complications can be attributed primarily to the complete disorganisation of the mechanism of pulmonary drainage produced during surgical interference by the state of anæsthesia, and in the post-anæsthetic period by the results of surgical interference.

Several occasional factors have been discussed which react with inefficient pulmonary drainage to intensify the risk of a post-operative pulmonary complication. Of these, pre-existing respiratory infection is the most potent, if the nature of the surgical condition permits, the anæsthetic should always be postponed until the subject has recovered from the infection. If this is not possible, much can be done during anæsthesia to reduce the risk of a post-operative pulmonary complication, not only when naso-bucco-pharyngeal or minor respiratory infection is present, but also in wet lung cases. The volume and viscosity of reflex secretion can be reduced to minimal proportions by adequate premedication, cocainization of the naso-bucco-pharynx and larynx and a swift and trouble-free induction to the level of complete sensory loss. If anæsthesia is maintained at the level of complete sensory loss, anoxia is avoided and the nitrogen-air cell scaffold is retained; in the absence of cardiovascular distress, secretion will not accumulate, but in wet lung cases, posture, suitable packing and suction must be added to the above measures to prevent the accumulation and spread of secretion during anæsthetic maintenance.

administration which may produce respiratory obstruction in a subject exposed to an atmosphere containing oxygen at an adequate partial pressure have been discussed in the previous section. It has been seen, too, that anoxia produced by simple asphyxiation is likely to occur only with the two weak anæsthetic gases, nitrous oxide and ethylene—which react as simple asphyxiants only when they are made to exclude oxygen from the atmosphere breathed, in a misguided attempt to obtain a deeper level of anæsthetic depression than they can give. Whether anoxia is produced by respiratory obstruction or by the simple asphyxiation, it first stimulates and then depresses the cardiovascular system. Stimulation is an unsuccessful attempt to compensate for oxygen-lack and is followed—when the vital medullary centres are depressed and when the increased volume of coronary blood flow can no longer keep pace with the lowered oxygen content of circulating blood—by cardiovascular collapse which is rapidly fatal. Wiggers (1941) divides the effects of anoxic anoxia on the cardiovascular system of Man into three stages, and his description is applicable to the course of anoxia during all types of anæsthesia.

During the first stage, when the oxygen content of inspired air is gradually reduced to about 12 per cent (91 mm. of mercury) the heart rate is gradually increased, for the S-A node is very sensitive to anoxia, and impulse formation at the S-A node is quickened for a brief period. The volume of coronary blood flow is materially increased, the period of ventricular contraction becomes shorter, the force of its contraction is increased, and venous pressure is slightly reduced. These effects combine to increase the cardiac output, and, when this is coupled with the stimulating effect of oxygen lack upon the vasomotor centre and its stimulation of the vital medullary centres through the medium of the chemoreceptors in the arch of the aorta and the carotid bodies, an increased systolic pressure is to be anticipated and does in fact occur.

The second stage, which Wiggers terms true anoxia, occurs when the oxygen content of inspired air falls below 12 per cent. In this event, it is observed that the rate and the stroke volume of the heart is further increased, the period of systole is gradually diminished and the effective venous pressure is progressively

the development of a pulmonary complication which will often fail to respond to appropriate treatment; this is particularly so in the aged. Hence, it is axiomatic, especially in aged and feeble subjects, that an indispensable measure in the prevention of a fatal post-operative pulmonary complication is the support of the cardiovascular system during anæsthesia and in the post-anæsthetic period.

The Cardiovascular System. In this discussion, emphasis has been laid throughout on the necessity of maintaining an efficient circulation during anæsthesia. While the anæsthetist can effectively substitute for the cessation of the mass movement of gases by lung ventilation, nothing can replace mass movement by circulating blood. Hence, anything which depresses the cardiovascular system during anæsthesia is a factor of the greatest importance, for mass movement by circulating blood is essential for the uptake and the excretion of respiratory and anæsthetic gases and vapours and for the detoxication and/or the excretion of non-volatile anæsthetics.

The functional activity of the cardiovascular system may be depressed during anæsthesia in a number of ways. Anoxia rapidly depresses the cardiovascular system and unless relieved soon produces cardiac failure; when the standard sequence of depression obtains, anæsthetic overdose produces cardiovascular distress and, unless it is relieved, secondary cardiac failure occurs. In the absence of anoxia and/or overdose, factors which diminish the return of venous blood to the right heart at length produce a deficient cardiac output and cardiac failure may occur. When overpressure is used with anæsthetics whose oil/water partition coefficient is high, primary cardiac failure may occur. And finally, when all these errors and accidents are avoided, appropriate stimulation during too-light anæsthesia may produce reflex arrythmias, and arrythmias may occur in the absence of external stimulation during surgical anæsthesia. In each instance these arrythmias may produce cardiovascular distress and/or cardiac arrest. It is proposed to discuss in turn the mechanism of each of these several types of cardiovascular depression.

The most potent and perhaps the commonest cause of cardiovascular distress during anæsthesia is anoxia, caused by respiratory obstruction or by simple asphyxiation. The pre-existing conditions of the subject and the errors or accidents of anæsthetic

the vasomotor and cardiac centres. At this stage oxygen insufflation carried out through a clear airway produces rapid recovery in a healthy subject. If, however, anoxia is not rapidly relieved, the vasomotor and in turn the cardiac centre are soon depressed and the subject enters Wiggers' third stage of anoxia; a circulatory crisis rapidly develops and fatal cardiac failure occurs. Thus, anoxia at first depresses the control exercised by the central nervous system on the cardiovascular system and ultimately exerts a local effect upon the heart itself which is the terminal event in cardiac failure.

In an adequately oxygenated subject, overdose with those blood-borne anæsthetics which produce the standard sequence of anæsthetic depression at length results in the depression of the respiratory centre and breathing ceases. The subject soon enters Wiggers' second stage of anoxia; and the vasomotor and the cardiac centres, although embarrassed by anoxia and anæsthetic overdose, still function. Because there is an effective circulation at this stage, the insufflation of oxygen through a clear airway results in rapid recovery, for the depressing action of anoxia is soon abolished and the excretion of the inhalation anæsthetic and the deviation and detoxication and/or excretion of non-volatile anæsthetics soon reduces the concentration of the anæsthetic in the vital medullary centres below the minimal threshold concentration necessary to depress them. If, however, anæsthetic overdose is not rapidly corrected a circulatory crisis rapidly develops and fatal cardiac failure occurs. This effect is produced by the depression of the vital medullary centres by anoxia and anæsthetic overdose and ultimately by the local effect of anoxia upon the heart itself. This sequence of events will be recognised as secondary cardiac failure.

The sequence of absorption of those anæsthetics whose oil/water partition coefficient is greater than unity and less than 14 indicates that they depress the body in the standard anæsthetic sequence and produce death by secondary cardiac failure. While this is without doubt their dominant action, it is of the utmost importance to ascertain whether each or any of them possess side-actions which exert a local action on the heart itself. From this point of view, it is proposed to discuss the action of each member of this group, which consists of the intravenous barbiturates, the

reduced. The early stimulation of the vasomotor centre now gives place to progressive depression and peripheral resistance is diminished. Because of the increased cardiac output and diminished peripheral resistance, the systolic blood pressure is maintained or gradually falls, the pulse pressure is unchanged or is gradually reduced, and the pulse rate continues to rise.

A circulatory crisis is obviously approaching and when during Wiggers' third stage of anoxia the oxygen content of inspired air falls to 7 per cent. (53 mm. of mercury) or below this figure, impulse formation at the S-A node is progressively slowed, and the conduction time of the bundle of His—as shown by the lengthening of the P-R interval—is slowed; but the most common effect of severe anoxia is a disturbance of the S-T segment with an inverted T-wave and this is of grave significance. It indicates severe cardiac damage and is often accompanied by other cardiac arrythmias while the duration of systole and cardiac output are still further diminished. Intense anoxia is also thought to produce severe myocardial depression, for in anoxic subjects the intravenous injection of adrenaline in therapeutic dosage does not sensitize the heart or produce ventricular fibrillation. Thus, despite increased coronary blood-flow, anoxia and diminished venous return to the right heart progressively reduce cardiac output. But vasomotor tone is also failing; and, in consequence of the reduced cardiac output and diminished peripheral resistance, the systolic and diastolic pressures continue to fall, and the pulse pressure is progressively reduced. At length the systolic blood pressure falls to zero and cardiac action ceases.

Anoxia produces the standard sequence of depression of the brain with secondary cardiac failure during all types of anæsthesia. Cardiac arrest is produced by anoxia in anæsthetised subjects more rapidly than in normal subjects, and the onset of cardiac failure is further accelerated if an uncompensated valvular lesion is present or if the cardiac reserve of the subject is impaired by disease In the absence of other factors, when anoxic anoxia of sufficient intensity is allowed to act during anæsthesia, the brain is depressed in the standard sequence, and at length the respiratory centre is depressed and breathing ceases. The subject is now in Wiggers' second stage of anoxia and the cardiovascular system although embarrassed functions effectively and responds to the control of

level for a short period of time. These effects tend to confirm the view that pentothal and evipan depress the body in the standard anæsthetic sequence and produce death by secondary cardiac failure.

If evipan or pentothal is injected intravenously at a rapid rate into a subject whose ability to clear these barbiturates from circulating blood is materially retarded, it is possible that their concentration in circulating blood may reach an effective concentration for the heart. When Kennedy and Narayana (1935) perfused frog's heart with evipan, they found that a 1 - 4000 solution of evipan immediately increased the rate and reduced the output of the heart by 10 per cent. The heart was arrested in about ten minutes by a 1 - 1000 solution of evipan but still responded to light mechanical stimulation; and when the heart was perfused with a 1 - 500 solution of evipan, permanent arrest of the heart was produced in about two minutes. There is no doubt that evipan or pentothal in a sufficient blood concentration can depress the functional activity of the heart by its local action on this organ, but blood concentrations of evipan or pentothal comparable with even the lowest concentration used in this perfusion experiment are seldom approached in clinical anæsthetic practice. If achieved, they could not be maintained for any appreciable time with the dosage used in clinical practice, provided that detoxication was within the limits of normality. Thus, 0·5 gm. of evipan or pentothal given intravenously in single dosage is sufficient for anæsthetic induction and for most minor surgical procedures; 1 gm. is often employed intravenously in single dosage in clinical practice and when these barbiturates [illegible] it is a rare ever[illegible] ½ - 2 hours. If [illegible] be 9 litres, then [illegible] pro-duced by the intravenous injection of 2 gm. in one minute, of 1 gm. in 30 seconds or 0 5 gm. in 15 seconds. But this takes no account of the rapid dilution, detoxication and deviation to non-nervous tissues which occurs immediately these barbiturates have been injected intravenously. Thus, even when these barbiturates are injected rapidly in single standard dosage, their blood concentration is unlikely to approach 1 - 4500 solution and its dilution is

ethers, nitrous oxide, ethylene and—probably—ethyl chloride and avertin.

When a swift and trouble-free induction to the level of depression of the respiratory centre is achieved in a healthy subject by the rapid intravenous injection of 0·5 gm. of pentothal or evipan, breathing ceases. The systolic blood-pressure may fall by about 10 - 20 mm. of mercury, and the pulse-rate may increase by about 10 - 15 beats per minute, but cardiac arrythmias are conspicuous by their absence. If at this point anoxia is prevented by the insufflation of oxygen through a clear airway, breathing usually re-commences within 30 - 60 seconds and the blood-pressure and pulse-rate rapidly return to their resting level. If, however, errors or accidents prevent adequate oxygenation, death from secondary cardiac failure may rapidly occur.

Pentothal and evipan have an oil/water partition coefficient of 4 - 5 and this indicates that they depress the body in the standard anæsthetic sequence. The administration of pentothal as described above can be likened to the use of overpressure with di-ethyl ether: and it is seen that despite the very rapid production of a level of anæsthetic depression sufficient to depress the respiratory centre, cardiac arrythmias do not occur, and the depression of the cardiovascular system which occurs is indicative of a relative depression of the vasomotor centre rather than a significant direct action of the barbiturate upon the heart itself. The slight fall of systolic blood-pressure and the small rise of pulse-rate can be attributed to the relative depression of the vasomotor centre together with a slight diminution of venous return to the right heart; and these effects, which are transitory, combine to increase the heart rate and to decrease its output with a consequent fall of blood-pressure. Since the metabolic rate is low and because oxygen insufflation was practised through a clear airway, anoxia is not a relevant factor; and, with the rapid deviation of the barbiturate from the vital medullary centres to non-nervous tissue and because anoxia is not acting, the vital medullary centres soon recover their full functional activity Hence, the cardiovascular system soon returns to its resting level, breathing re-commences and, as it increases in depth and the negative intrapleural pressure on inspiration rises, so the venous return to the right heart increases, cardiac output rises, and the systolic blood pressure may rise above its resting

skin dilate. Herrick *et al.* (1932) produced evidence to show that a local vasodilatation occurs in the extremities, and Mann *et al.* (1935) observed an increased blood flow in the peripheral capillaries during light di-ethyl ether anæsthesia. Sollman (1936) stated that the cerebral capillaries dilate and Derouaux (1909) observed that the intestinal capillaries are constricted during di-ethyl ether anæsthesia. Thus, vasodilatation occurs during the early stages of di-ethyl ether anæsthesia, and the heart rate and cardiac output increases. There is a slight rise of blood-pressure and this indicates that on balance the cardiovascular system is stimulated.

Beecher (1940) states that respiration invariably fails before the heart during di-ethyl ether anæsthesia. Reference to Table 27 will indicate that the brain absorbs di-ethyl ether more rapidly than does the heart; when this is coupled with its clinical behaviour when overpressure is used in clinical anæsthetic practice, one is constrained to be more dogmatic even than Beecher, and to assert that primary cardiac failure produced by anæsthetic overdose cannot occur during di-ethyl anæsthesia.[1] It can be concluded that di-ethyl ether produces the standard sequence of anæsthetic depression, and overdose with this agent produces death from secondary cardiac failure. Moreover, the opinion almost universally held by clinicians that di-ethyl ether is a cardiovascular stimulant appears to be justified.

Di-vinyl ether is a potent inhalation anæsthetic, more volatile and less irritating to the respiratory tract than is di-ethyl ether. The value of its oil/water partition coefficient is still in dispute. On the one hand Kockmann (1936) believes it to be of the same order as that of di-ethyl ether, and Leake and Chen (1930) observed it to be 2 5; on the other hand, Adriani (1946) gives 41·3 as the value of this index for di-vinyl ether. The pattern of behaviour of di-vinyl ether in clinical practice is similar to that of di-ethyl ether and bears no resemblance to that of cyclopropane, whose oil/water partition coefficient is 43. This in turn suggests that the oil/water partition coefficient of di-vinyl ether is not high; in this discussion the figure of Leake and Chen, viz. 2·5 is accepted as more likely to be the correct value.

[1] Evidence is discussed later which indicates that reflex effects during light di-ethyl ether anæsthesia can produce primary cardiac failure.

very rapid. Moreover if mal-administration produced an abnormally high concentration of evipan or pentothal in circulating blood, the uptake of these barbiturates by the heart is slow, relative to the rate of their uptake by the brain, for they have an oil/water partition coefficient of about 5. And when evipan or pentothal is injected intravenously into a healthy subject in standard dosage at a proper rate, the probability of these barbiturates producing a local effect upon the heart is very remote; in clinical anæsthetic practice cardiovascular effects can be attributed solely to the anæsthetic depression of the vital medullary centres or to anoxia. Thus, the cardiovascular system of a soldier, with acute amœbiasis of the liver who became comatose after a single intravenous injection of 0·7 gm. of pentothal and remained so for 22 hours, was depressed; but with oxygen therapy the circulatory rate was sufficiently effective to permit him to recover from what must have been an abnormally high and prolonged blood concentration of pentothal. It can be concluded that evipan and pentothal do not produce a local effect upon the cardiovascular system in the conditions which obtain in clinical anæsthetic practice. They depress the body in the standard anæsthetic sequence, and, when overdose is produced, death occurs from secondary cardiac failure.

Di-ethyl ether is a potent inhalation anæsthetic with a pungent odour whose oil/water partition coefficient is 2·3. Evidence has been discussed which shows that it produces the standard sequence of anæsthetic depression even when gross overpressure is employed; and when at length anæsthetic overdose occurs with this anæsthetic agent, the vital medullary centres are depressed in standard sequence and death occurs from secondary cardiac failure.

There is ample evidence that di-ethyl ether in a sufficient concentration depresses heart muscle in a graded manner; it is just as clear that di-ethyl ether, in the concentrations used in clinical anæsthetic practice, does not depress but on the contrary stimulates the cardiovascular system Thus, Blalock (1927, 1928) observed in dogs during the early stages of di-ethyl ether anæsthesia that the heart rate increased, cardiac output was augmented and there was a slight rise in the mean blood-pressure. Pilcher and Sollman (1915) showed that the vasomotor centre was not directly stimulated during di-ethyl ether anæsthesia but that the capillaries of the

with ethyl chloride. In 1929, Hornabrook (who was the writer's tutor in anæsthetics) reported a series of 75,000 ethyl chloride anæsthetics with only two deaths; and the writer himself has given ethyl chloride on 10,610 occasions without a death. When one considers the ease with which inadvertent overpressure can occur with ethyl chloride, Hornabrook's figures are inconceivable—however careful and skilful the administrator—if the sequence of absorption was such that ethyl chloride could produce primary cardiac failure. Minnett and Gillies (1944) state that the oil/water partition coefficient of ethyl chloride is high—which suggests primary cardiac failure as the mechanism of cardiac arrest. Reference to Table 17, however, shows that the relative solubility of ethyl chloride in water and in whole blood is of the same order as that of nitrous oxide in these two solvents. This suggests an oil/water partition coefficient of the same order, and indicates that ethyl chloride is absorbed in the standard anæsthetic sequence and produces death from secondary cardiac failure.

The same disagreement is seen in the reported effects of ethyl chloride on the pulse-rate and blood-pressure. McCardie (1906), and Rood and Webber (1929) stated that the pulse-rate slowed and the blood-pressure fell during ethyl chloride anæsthesia. Hornabrook (1929) observed no significant alteration of the pulse-rate, which increased or decreased by about ± 4 beats per minute· the systolic blood-pressure rose by 4 — 12 mm. of mercury. In the absence of anoxia and excitement, and if overdose is avoided, the present writer's observations coincide with those of Hornabrook; but he is of the opinion that the rise of pulse-rate and blood-pressure is *not* due to ethyl chloride and is consistent with the *increase of the carbon dioxide* content of inspired air produced by the rebreathing which is invariably used during ethyl chloride induction.

In the absence of accurate knowledge of the oil/water partition coefficient of ethyl chloride, and because it is used for anæsthetics of short duration, it is not possible to assess accurately the mechanism of its action on the cardiovascular system. The data examined have led the author to the opinion that ethyl chloride produces the standard sequence of anæsthetic response and causes death by secondary cardiac failure, and that the cardiovascular system is not significantly depressed if anoxia and anæsthetic

action of this anæsthetic upon the heart itself. Luckhardt and Carter (1923) observed that the vasomotor centre is not depressed and the blood pressure is not significantly changed during ethylene anæsthesia. It can be concluded that ethylene does not depress the functional activity of the cardiovascular system in the conditions of clinical anæsthetic practice. As with nitrous oxide, so also with ethylene, the cardiovascular system can be depressed, only if anoxia is permitted to act during anæsthesia: in this event, death occurs from secondary cardiac failure.

Ethyl chloride is a very potent anæsthetic gas below its critical temperature, for its boiling point at mean sea level is 12·5 degrees Centigrade. It is supplied for use in clinical practice, slightly compressed, as a liquid in glass phials. When released from its container, each cubic centimetre of liquid instantly forms about 445 c.c. of ethyl chloride vapour at room temperature; because of this, a very high partial pressure of ethyl chloride can inadvertently be produced in the anæsthetic atmosphere. Since it is non-irritating to the respiratory tract, overpressure results in the very rapid uptake of ethyl chloride, and, because it is a very potent anæsthetic, inadvertent or ill-controlled overpressure can readily produce anæsthetic overdose. Rood and Webber (1929) state that anæsthetic depression of the respiratory centre can be produced in one minute.

As with the intravenous barbiturates, induction with ethyl chloride is so rapid that reflex cardiac effects are unknown and death occurs from simple asphyxiation or from anæsthetic overdose. For the same reason it is difficult to decide whether overdose produces primary cardiac failure or whether secondary cardiac failure occurs with respiratory failure preceding cardiac arrest. This is shown in the conflicting reports of its clinical behaviour. On the one hand, Beecher (1940) states that ethyl chloride produces harmful cardiac effects similar to those caused by chloroform. Henderson and Kennedy (1930) in a review of twenty-six deaths during ethyl chloride anæsthesia concluded that seven deaths were cardiac in origin, two were respiratory, twelve were cardiac and respiratory, three were asphyxial and in two cases the cause of death could not be ascertained. On the other hand, Hewitt (1922) and Rood and Webber (1929) believed that respiratory arrest always preceded cardiac failure when overdose occurred

and with di-ethyl and di-vinyl ether produces death from secondary cardiac failure; and it is probable that ethyl chloride [illegible] equately [illegible] ed with [illegible] al anæs- [illegible] of com- [illegible] any of the five aforementioned anæsthetics significantly depress the functional activity of the cardiovascular system. In the absence of anæsthetic overdose, anoxic anoxia of sufficient intensity and duration will rapidly produce death from secondary cardiac failure during anæsthesia with all these agents. Hence with these seven anæsthetics if the subject is protected from external stimulation, death during anæsthesia always takes the form of secondary cardiac failure. The importance of these conclusions cannot be over-estimated, for secondary cardiac failure gives ample warning of impending disaster — a fact that enhances the value of these anæsthetics in clinical practice.

There is another mechanism acting during anæsthesia which may produce secondary cardiac failure. It cannot be attributed to the action of particular anæsthetics and it results solely from the diminution of the minute-volume of venous blood returned to the right heart produced by the state of anæsthesia

The output of the heart—intimately related to blood-pressure—depends upon the force and frequency of the heart beat and upon the volume of venous return, for the heart can only pump as much blood as it receives from the great veins. Blood-pressure is the product of cardiac output and peripheral resistance. When shallow breathing and loss of muscle tone is produced during blood-borne anæsthesia, during spinal or local anæsthesia on the trunk and when d-tubo-curarine chlorine is used, the minute-volume of venous blood returned to the right heart is diminished, for muscle movement and the support afforded the veins by muscles in tone are abolished, and shallow breathing reduces the aspiration of venous blood to the right heart produced on inspiration by negative intrapleural pressure. Hence, a level of anæsthetic depression, producing muscular relaxation adequate for the needs of major surgical procedures but leaving cardiac action and vasomotor tone intact and active, inevitably reduces the minute-volume

overdose are avoided. Its danger lies in the rash or ignorant use of excessive overpressure and Flagg (1922) says that collapse is more likely to follow ethyl chloride than any other anæsthetic.

When avertin is administered rectally in basal dosage to a healthy subject, anoxia being avoided, the pulse-rate and blood-pressure fall to the basal level for the subject; slight and insignificant deviations from normal may occasionally be recorded electrocardiographically if minor degrees of respiratory obstruction are allowed to occur. If, however, liver inefficiency is present or if greater than basal dosage is used, an avertin blood concentration higher than 9 mgs. per cent. is readily produced and—in the absence of anoxia—the pulse-rate and blood-pressure fall below the resting level and the pulse becomes soft, full and slow. When an isolated rabbit's heart was perfused with avertin solution, Parsons (1929) found that a 1 - 5000 solution produced cardiac stimulation which was immediately followed by slowing and diminished force of contraction of the heart. Coronary dilatation followed by cardiac arrest was produced by 1 - 1250 solution of avertin within five minutes. These concentrations of avertin are, respectively, more than twice and almost eight times that required to produce basal anæsthesia in Man, viz. 9 mgs. per cent. Hence, if basal dosage in used in subjects whose ability to detoxicate this non-volatile anæsthetic has not been impaired, and—anoxia being avoided throughout—avertin does not depress the cardiovascular system in clinical practice.

Although no data of the oil/water partition coefficient of avertin can be found, there is reason to believe that it produces the standard sequence of anæsthetic response when used in basal dosage Clinical experience tends to confirm this view. Except for one doubtful case reported by Beecher (1939), no hint of primary cardiac failure with avertin has been found in anæsthetic literature, and in 3,000 cases anæsthetised with avertin, the writer has observed nothing to suggest that avertin can produce a distortion of the standard sequence of anæsthetic response. Until evidence to the contrary is forthcoming, it can be safely assumed that avertin cannot produce primary cardiac failure in Man, if basal dosage is used in subjects who can efficiently detoxicate this non-volatile anæsthetic.

It can be concluded that overdose with evipan and pentothal

its rate of intake must be progressively increased until the pulse-rate falls to 80 - 90 beats per minute: and this, *and only this*, is the proper rate of intake for the particular subject. By this means the deficient venous return, which sooner or later must inevitably occur during prolonged major surgical procedures, can be effectively prevented: this in turn makes major surgical operations, lasting for five hours and more, clinically possible. It is thought, too, that the support which this measure affords the cardiovascular system during prolonged surgical procedures, is instrumental in reducing the incidence of cerebral vascular catastrophies in the post-anæsthetic period.

Recently, however, in order to secure the utmost hæmostasis in certain surgical procedures, Griffiths and Gillies (1948) and Gardner (1946) have advocated measures which reduce cardiac output, diminish the blood pressure, and curtail bleeding. In view of the deleterious effects of deficient venous return discussed above, it is imperative to examine the merits and demerits of the production of hæmostasis by controlled hypotension.

Griffiths and Gillies produce an almost bloodless operative field for thoraco-lumbar splanchnicectomy and sympathectomy with a differential spinal nerve block which aims " to produce a total sympathetic nerve block and lesser degrees of sensory and motor paralysis . . . . leaving the respiratory muscles and medullary centres unaffected." They inject intrathecally 150 - 250 mgs. of procaine dissolved in 3 - 4 c.c. of cerebrospinal fluid at the level of the second lumbar interspace. The subject is placed in the supine position, the table is immediately tilted into a steep Trendelenburg position, and an oxygen atmosphere is administered through a clear airway. With the paralysis of vasoconstrictor nerves, the blood-pressure falls rapidly and in ten to twenty minutes the radial pulse is impalpable and sphygmomanometer readings of blood-pressure cannot be obtained. The apex beat is palpable and the heart rate is 40 - 50 beats per minute. The capillary response to pressure is brisk and the subject's colour is usually a bright pink. As is to be expected with procaine, this clinical state is maintained for twenty to thirty minutes, after which the cardiovascular system gradually returns to normal. It is to be noted that the period of hypotension is relatively short and that adequate oxygenation is maintained throughout; and these

of blood returned to the right heart and cardiac output is correspondingly reduced. Since the metabolic rate of the subject is also reduced, this diminution of cardiac output produced by a reduced venous return at first produces little, if any, embarrassment of the cardiovascular system. If, however, loss of muscle tone and shallow breathing are unduly prolonged, the minute-volume of venous blood returned to the right heart at length reaches a critically low level, cardiac output soon falls below the needs of even the low metabolic rate of the subject and the vicious circle of fall of blood-pressure and anoxia is initiated. The time required to initiate this sequence varies between subjects. In an adequately oxygenated healthy subject it commonly occurs when complete muscular relaxation has been maintained for between one and a half and two and a half hours, but hæmorrhage will accelerate its onset. In a subject with a pathologically high blood-pressure, it can occur after only thirty minutes' anæsthesia to this level of depression; and again, hæmorrhage, surgical shock or any factor which reduces the volume of circulating blood will materially hasten its onset.

The first clinical sign of the onset of deficient venous return in an adequately oxygenated subject, anæsthetised to a level which abolishes reflex effects, is a rise of the pulse rate. As in paroxysmal tachycardia, so also in this condition an increase in the frequency of the heart beat serves no useful purpose, for diastole is short, each beat is small and the minute-output of the heart is not increased. On the contrary, if the anæsthetist fails to comprehend the import of this rising pulse rate, or if he ignores it, there is added to the progressive increase in the frequency of the heart-beat, a gradual fall of blood-pressure, and inadequate oxygenation of the subject soon becomes apparent. At first, adequate oxygenation can be achieved by assisted respiration with an oxygen atmosphere, but, as the circulatory rate and the blood-pressure progressively fall, assisted respiration with an oxygen atmosphere is progressively less effective. At length it fails to compensate for the stagnant anoxia, and the subject dies from secondary cardiac failure The onset of this sequence of events can be prevented—or it can be aborted when it does occur—by the intravenous administration of fluid, preferably whole blood, at a proper rate. It is not sufficient to give whole blood intravenously;

its rate of intake must be progressively increased until the pulse-rate falls to 80 - 90 beats per minute: and this, *and only this*, is the proper rate of intake for the particular subject. By this means the deficient venous return, which sooner or later must inevitably occur during prolonged major surgical procedures, can be effectively prevented: this in turn makes major surgical operations, lasting for five hours and more, clinically possible. It is thought, too, that the support which this measure affords the cardiovascular system during prolonged surgical procedures, is instrumental in reducing the incidence of cerebral vascular catastrophies in the post-anæsthetic period.

Recently, however, in order to secure the utmost hæmostasis in certain surgical procedures, Griffiths and Gillies (1948) and Gardner (1946) have advocated measures which reduce cardiac output, diminish the blood pressure, and curtail bleeding. In view of the deleterious effects of deficient venous return discussed above, it is imperative to examine the merits and demerits of the production of hæmostasis by controlled hypotension.

Griffiths and Gillies produce an almost bloodless operative field for thoraco-lumbar splanchnicectomy and sympathectomy with a differential spinal nerve block which aims " to produce a total sympathetic nerve block and lesser degrees of sensory and motor paralysis . . . . leaving the respiratory muscles and medullary centres unaffected." They inject intrathecally 150 - 250 mgs. of procaine dissolved in 3 - 4 c.c. of cerebrospinal fluid at the level of the second lumbar interspace. The subject is placed in the supine position, the table is immediately tilted into a steep Trendelenburg position, and an oxygen atmosphere is administered through a clear airway. With the paralysis of vasoconstrictor nerves, the blood-pressure falls rapidly and in ten to twenty minutes the radial pulse is impalpable and sphygmomanometer readings of blood-pressure cannot be obtained. The apex beat is palpable and the heart rate is 40 - 50 beats per minute. The capillary response to pressure is brisk and the subject's colour is usually a bright pink. As is to be expected with procaine, this clinical state is maintained for twenty to thirty minutes, after which the cardiovascular system gradually returns to normal. It is to be noted that the period of hypotension is relatively short and that adequate oxygenation is maintained throughout; and these

observers state that "gravitational drainage of venous blood ensures adequate cardiac filling which is essential in these cases where the blood pressure is usually unrecordable for some time." Observers conversant with high spinal anæsthesia, with perhaps an anterior splanchnic block, for major upper abdominal surgery are aware of this state of hypotension in which sphygmomanometer readings serve no useful purpose; they will agree that the Trendelenburg position to ensure adequate venous return, and the use of appropriate oxygen therapy are measures indispensable to the subject's safety. Vehrs (1931) asserts that the Trendelenburg position is necessary to prevent fatal cerebral anæmia and to assist venous return to the heart; and Griffiths and Gillies state: "It must be emphasised that such a method (of total hypotension) is safe only when circumstances permit the patient to be kept in the Trendelenburg position."

Gardner (1946) describes a case of a large vascular meningioma situated in the olfactory groove in which ablation of the tumour promised to be difficult and tedious because of expected bleeding. The subject was anæsthetised with intravenous pentothal, and, after arterial puncture, 1600 c.c. of blood was drawn off into a container and mixed with appropriate heparin. The systolic blood-pressure fell from 140 to 100 mm. of mercury and the pulse-rate rose from 130 to 140 beats per minute. There was little bleeding during surgical interference, which was therefore shorter and lasted for two and a half hours When surgical interference ceased, the blood-pressure was 90 mm. of mercury and rose to 120 mm. of mercury when 1100 c.c of the heparinized blood was replaced. After the patient had been settled in bed the blood-pressure rose to 150/100 mm. of mercury and the pulse-rate fell to 120 beats per minute. This can truly be termed controlled hypotension, for Gardner aims to maintain a minimal systolic blood-pressure of 90 mm. of mercury and, moreover, blood can be returned at will when the condition of the subject demands. This controlled hypotension differs from the total hypotension of Griffiths and Gillies in its intensity, which is relative, and its duration, which is prolonged. It is thought that the controlled hypotension produced by Gardner is a justifiable procedure for the type of surgery that he describes.

There is as yet insufficient clinical evidence on which to assess the value of deliberately produced hypotension as an aid to surgery. One's first reaction is to condemn it out of hand. Intentionally to impair the efficiency of the cardiovascular system would appear to be not only a contravention of first principles but also the subordination of the patient's safety to the surgeon's convenience. But Griffiths and Gillies have shown in a small series of cases that total hypotension for short periods of time can be safely carried out; and Gardner's controlled hypotension undoubtedly has a real value in a small special group of surgical cases. Except in the type of surgery described by Gardner, it is the present writer's opinion that hypotension in the interest of hæmostasis is an unjustifiable procedure, for a bloodless surgical field can be produced locally by the use of vasoconstrictors.

Efficient local hæmostasis can be produced by the infiltration of the operative field with 1 - 200,000 adrenaline. When this method of producing a bloodless operative field is used with anæsthetics such as di-ethyl ether, whose oil/water partition coefficient is less than 14, the efficiency of the cardiovascular system is unimpaired; Orth *et al.* (1939), using comparable dosage of adrenaline in dogs during di-ethyl ether anæsthesia, confirmed this clinical opinion. The use of adrenaline during chloroform anæsthesia is known to produce arrythmias and/or primary cardiac failure and it has been assumed that its use during cyclopropane and trichlorethylene anæsthesia produces a like effect, for these two anæsthetics also have a high oil/water partition coefficient. As a result of his work on dogs, Meeks (1940) concludes that adrenaline is absolutely contra-indicated during cyclopropane anæsthesia. *Evidence has been discussed, however, which indicates that the* heart is not rendered susceptible to adrenaline excess during cyclopropane and trichlorethylene anæsthesia at the level of complete sensory loss or lighter; but at deeper levels of anæsthetic depression there is little doubt with both anæsthetics that adrenaline produces cardiac arrythmias and/or primary cardiac failure. Nowadays, when d-tubo-curarine chloride is used to produce muscular relaxation, anæsthesia to the level of complete sensory loss is the deepest level of anæsthetic depression desired or required in clinical practice. This in turn suggests that an efficient, safe, anæsthetic preparation, with a bloodless surgical field locally, can

be produced if the local infiltration of 1 - 200,000 adrenaline is combined with d-tubo-curarine chloride and cyclopropane anæsthesia not deeper than the level of complete sensory loss. This is in fact so, for adrenaline 1 - 200,000 has been used by the writer's surgical colleagues during the last five years, without incident, to produce effective local hæmostasis during cyclopropane anæsthesia not deeper than complete sensory loss. In spite of this clinical evidence it is generally accepted that adrenaline should not be used during trichlorethylene anæsthesia, for the physical properties of this agent render it less controllable than cyclopropane.

It can be concluded that adrenaline should never be used during chloroform or trichlorethylene anæsthesia. With all the other anæsthetics in common clinical use whose oil/water partition coefficient is less than 14, and with cyclopropane anæsthesia not deeper than complete sensory loss, efficient local hæmostasis can be safely produced by the infiltration of the surgical field with 1 - 200,000 adrenaline. Orth *et al.* (1939) compared the ability of adrenaline and several other sympathomimetic amines to produce cardiac arrythmias during anæsthesia. Neosynephrin, a potent vasoconstrictor which unfortunately is not yet available in this country, was the only substance examined which did not produce cardiac arrythmias during deep cyclopropane anæsthesia. These data indicate that local hæmostasis can be safely produced with 1 - 200,000 adrenaline during clinical anæsthesia and suggest that absolute safety would be attained if this local hæmostasis was produced with neosynephrin.

In contra-distinction to the pattern of behaviour of the seven anæsthetics discussed above, overdose with the four anæsthetics now to be considered—namely, chloroform, cyclopropane, trichlorethylene and trichlorethyl alcohol — may produce death from primary cardiac failure. Cardiovascular distress during anæsthesia with these four agents is of the gravest import, for warning of impending disaster is often absent; measures taken to arrest the onset of primary cardiac failure are generally initiated too late to be effective while resuscitation of the subject when cardiac arrest of this nature has occurred is seldom successful.

Chloroform is a potent anæsthetic vapour with a pleasant penetrating odour; its oil/water partition coefficient is 64. Unlike di-ethyl ether, chloroform in the concentrations used in clinical

practice depresses the functional activity of the cardiovascular system. Blalock (1928) showed that chloroform reduced the cardiac output of dogs by an average of 30 per cent. and Bayliss (1908) and Pilcher and Sollman (1915) observed a diminished peripheral resistance during chloroform anæsthesia. Hence, chloroform not only reduces cardiac output but also diminishes peripheral resistance, and a fall of blood-pressure is observed during the early stages of chloroform anæsthesia which is intensified as anæsthesia deepens. The soft, full pulse of chloroform is in marked contrast to the firm, bounding pulse of di-ethyl ether anæsthesia.

In clinical practice, a graduated method of induction with chloroform produces the standard sequence of anæsthetic response; anæsthetic overdose at length depresses the vital medullary centres in the standard sequence and death occurs from secondary cardiac failure. The control of the partial pressure of this potent anæsthetic vapour in the anæsthetic atmosphere however is a matter of some difficulty. Chloroform is relatively insoluble in whole blood, and in a subject breathing a chloroform atmosphere of constant composition, the mass of chloroform absorbed by blood flowing in the pulmonary capillaries per unit-time produces an insignificant diminution in the partial pressure of chloroform in alveolar air. Hence, even minor alterations of the partial pressure of chloroform in the anæsthetic atmosphere are immediately reflected in its partial pressure in alveolar air, and, in turn, in its tension in solution in blood leaving the pulmonary capillaries. Since chloroform is a very potent anæsthetic vapour, it follows that a relatively small increase in its partial pressure in the anæsthetic atmosphere is immediately followed by a significant increase in the intensity of anæsthetic depression. A graduated method of induction is therefore a difficult procedure with chloroform, and the concentration of chloroform in blood leaving the pulmonary capillaries may—even when great care is exercised—inadvertently reach a dangerously high level.

When overpressure is inadvertently used and a dangerously high concentration of chloroform is produced in circulating blood, there must be added to the fall of blood-pressure, occurring normally during chloroform anæsthesia, cardiac arrythmias, ranging from extrasystoles to ventricular fibrillation and vagal

be produced if the local infiltration of 1 - 200,000 adrenaline is combined with d-tubo-curarine chloride and cyclopropane anæsthesia not deeper than the level of complete sensory loss. This is in fact so, for adrenaline 1 - 200,000 has been used by the writer's surgical colleagues during the last five years, without incident, to produce effective local hæmostasis during cyclopropane anæsthesia not deeper than complete sensory loss. In spite of this clinical evidence it is generally accepted that adrenaline should not be used during trichlorethylene anæsthesia, for the physical properties of this agent render it less controllable than cyclopropane.

It can be concluded that adrenaline should never be used during chloroform or trichlorethylene anæsthesia. With all the other anæsthetics in common clinical use whose oil/water partition coefficient is less than 14, and with cyclopropane anæsthesia not deeper than complete sensory loss, efficient local hæmostasis can be safely produced by the infiltration of the surgical field with 1 - 200,000 adrenaline. *Orth et al* (1939) *compared the ability* of adrenaline and several other sympathomimetic amines to produce cardiac arrythmias during anæsthesia. Neosynephrin, a potent vasoconstrictor which unfortunately is not yet available in this country, was the only substance examined which did not produce cardiac arrythmias during deep cyclopropane anæsthesia. These data indicate that local hæmostasis can be safely produced with 1 - 200,000 adrenaline during clinical anæsthesia and suggest that absolute safety would be attained if this local hæmostasis was produced with neosynephrin.

In contra-distinction to the pattern of behaviour of the seven anæsthetics discussed above, overdose with the four anæsthetics now to be considered—namely, chloroform, cyclopropane, trichlorethylene and trichlorethyl alcohol — may produce death from primary cardiac failure. Cardiovascular distress during anæsthesia with these four agents is of the gravest import, for warning of impending disaster is often absent; measures taken to arrest the onset of primary cardiac failure are generally initiated too late to be effective while resuscitation of the subject when cardiac arrest of this nature has occurred is seldom successful.

Chloroform is a potent anæsthetic vapour with a pleasant penetrating odour, its oil/water partition coefficient is 64. Unlike di-ethyl ether, chloroform in the concentrations used in clinical

It is significant, however, that sympathetic overaction or the intravenous injection of adrenaline does not produce ventricular fibrillation in cats during di-ethyl ether anæsthesia, and it can be concluded that chloroform anæsthesia renders the heart susceptible to the effect of sympathetic overaction or adrenaline. If the heart is to be rendered susceptible to sympathetic overaction as early in anæsthesia as the stage of non-cooperative stupor, the uptake [illegible] of chloroform by the heart must of [illegible] l's figures (1891) indicate that a high [illegible] can be achieved in the heart before full anæsthesia is established if overpressure is used during induction; this, it is thought, is the explanation of primary cardiac failure during light chloroform anæsthesia. And reference to Table 27 indicates that chloroform is absorbed by the heart more rapidly than by the brain. During a graduated induction the rapid uptake of chloroform by the heart is of no consequence, for its concentration never reaches an effective concentration for the heart. But if there is inadvertent overpressure, a concentration of chloroform can readily be achieved in the heart sufficient to depress the functional activity of that organ or to render it susceptible to the effects of sympathetic overaction—even as early in induction as the stage of non-cooperative stupor, when sympathetic overaction is likely to be most intense. And when primary cardiac failure occurs during the non-cooperative stupor stage of chloroform anæsthesia, it invariably takes the form of ventricular fibrillation and it is observed that overpressure and/or sympathetic overaction is always present.

In the past, primary cardiac failure during chloroform anæsthesia was often attributed to a vagal inhibition of the heart; with the introduction of atropine as a pre-anæsthetic medicant this form of primary cardiac failure has been reported in current literature with ever-diminishing frequency. In under-atropinized subjects, it seems reasonable to suggest that during the stage of anæsthetic sleep the para-sympathetic entities of the hypothalamus, freed from cortical control and the antagonising influence of the posterior and lateral hypothalamic nuclei, may produce vagal overaction in response to appropriate external stimulus. And if vagal overaction occurred in a heart in which overpressure had produced a high chloroform content, it is possible that the vagal escape mechanism

inhibition of the heart. These effects, which may terminate in cardiac arrest, occur in response to appropriate external stimulus, but they may also occur without obvious cause. During the non-cooperative stupor stage of chloroform anæsthesia, ventricular extrasystoles are common, and ventricular fibrillation may occur. Vagal inhibition of the heart may occur during the stage of light anæsthetic sleep. In a healthy subject, when the ability to react *in a reflex manner to external stimulus is abolished by chloroform* anæsthesia deeper than the stage of anæsthetic sleep but short of respiratory failure, cardiac arrythmias usually cease. But cardiac arrythmias of varying degrees of intensity may occur at this level of anæsthesia in subjects whose cardiac reserve is impaired, and they may lead to ventricular fibrillation unless the partial pressure of chloroform in the anæsthetic atmosphere is immediately reduced to zero.

In cats, Levy (1913) observed that the intravenous injection of adrenaline or appropriate external stimulus during light chloroform anæsthesia produced extrasystoles and ventricular fibrillation within a few seconds, and the local application of adrenaline to the heart itself produced the same result. Beattie *et al.* (1930) obtained the same result when the stellate ganglion or the cardio-accelerator nerves were stimulated during light chloroform anæsthesia. They also observed that stimulation of the hypothalamus produced cardiac arrythmias during chloroform anæsthesia; and, with Bard (1928), they found that the cardiac arrythmias of light chloroform anæsthesia were immediately abolished when the hypothalamus was ablated In clinical practice, it is observed that cardiac arrythmias and/or ventricular fibrillation occur most commonly during the non-cooperative stupor stage of chloroform anæsthesia when the sympathetic entities of the hypothalamus (namely, the posterior and lateral nuclear masses), freed from cortical control, may produce intense sympathetic overaction. It is observed, moreover, that these cardiac arrythmias are abolished in healthy, adequately atropinized subjects when chloroform anæsthesia deepens beyond the stage of non-cooperative stupor, for the posterior and lateral hypothalamic nuclei are now depressed and sympathetic overaction ceases. Hence, it can be concluded that sympathetic overaction is a precipitating cause of the cardiac arrythmias which may occur during light chloroform anæsthesia.

action of cyclopropane upon the heart itself. Table 27 indicates that cyclopropane, like chloroform, is absorbed by the heart more rapidly than by the brain taken as a whole. But its uptake differs from that of chloroform, for it has been concluded that the heart reaches anæsthetic equilibrium with a cyclopropane atmosphere soon after the areas of sensory co-ordination of the brain but more rapidly than the areas of motor co-ordination of the brain and its vital medullary centres. Thus, during light cyclopropane anæsthesia Waters (1936) showed that the heart was not affected by adrenaline injected intravenously and this indicates that the concentration of cyclopropane in the heart at this level of anæsthesia, has not rendered it susceptible to adrenaline excess. Clinical experience strengthens this view, for neither bradycardia, cardiac arrythmias nor primary cardiac failure are produced when overpressure is discretely used with cyclopropane to the level of complete sensory loss in a healthy subject; at this level of cyclopropane anæsthesia, the injection of adrenaline 1 - 200,000 for the purpose of hæmostasis, does not produce cardiovascular effects. During cyclopropane anæsthesia deeper than the level of complete sensory loss, however, adrenaline injected intravenously was shown by Waters (1936) to produce ventricular fibrillation; and the observations of Meeks, Hathaway and Orth (1937) indicate that the heart is abnormally sensitive to the effects of adrenaline at comparable levels of cyclopropane anæsthesia. In clinical anæsthetic practice, the inadvertent use of overpressure with cyclopropane at levels of anæsthesia deeper than complete sensory loss, often produces cardiac arrythmias in healthy subjects. Hence, it can be assumed at levels of cyclopropane anæsthesia deeper than complete sensory loss that the heart is in fact in anæsthetic equilibrium with the anæsthetic atmosphere. It therefore follows that the use of overpressure with cyclopropane is a dangerous procedure, and at levels of cyclopropane anæsthesia deeper than complete sensory loss overpressure must inevitably be followed by cardiac arrythmias which may end in ventricular fibrillation: for cyclopropane is poorly soluble in whole blood, and alterations in its partial pressure in the anæsthetic atmosphere are immediately reflected in its concentration in blood leaving the pulmonary capillaries and in turn in the heart itself. Since induction to the

would fail to re-establish normal cardiac action. The data available make it impossible wholly to accept or to reject vagal overaction as a possible mechanism of primary cardiac failure during chloroform anæsthesia when overpressure has been used in an under-atropinized subject. And it seems significant that this type of primary cardiac failure was reported in chloroform anæsthesia during the early stage of anæsthetic sleep and that its incidence has diminished since the introduction of atropine as a pre-anæsthetic medicant.

Primary cardiac failure during light chloroform anæsthesia serves to emphasise not only the rapid uptake of chloroform by the heart but also the deleterious results which may follow reflex effects produced by emotional and/or physical stress during light anæsthesia. When, however, autonomic overaction and the ability to react in a reflex manner to external stimulation are to all intent and purpose abolished by chloroform anæsthesia to the level of complete sensory loss, the possibility of primary cardiac failure is a remote one in a healthy subject, if this level of chloroform anæsthesia is not exceeded. In subjects whose cardiac reserve is impaired, however, cardiac arrythmias which are the precursors of primary failure may occur at this level of chloroform anæsthesia. Moreover, if overpressure is permitted to act in healthy subjects at the level of complete sensory loss, then to the fall of blood pressure which deep chloroform anæsthesia produces there must be added cardiac arrythmias; and ventricular fibrillation may occur unless the partial pressure of chloroform in the anæsthetic atmosphere is immediately reduced to zero.

Cyclopropane is a potent, non-irritating anæsthetic gas with an oil/water partition coefficient of 43. When a graduated method of induction is used with cyclopropane, the standard sequence of anæsthetic depression is produced. When, however, overpressure is employed with this anæsthetic, bradycardia is followed by cardiac arrythmias which have been identified as ventricular extra-systoles; and these cardiac irregularities may soon be followed by ventricular fibrillation unless the partial pressure of cyclopropane in the anæsthetic atmosphere is immediately reduced to zero. Hence, primary cardiac failure may occur during cyclopropane anæsthesia in clinical anæsthetic practice, and there is reason to believe that these cardiovascular effects are produced by the direct

action of cyclopropane upon the heart itself. Table 27 indicates that cyclopropane, like chloroform, is absorbed by the heart more rapidly than by the brain taken as a whole. But its uptake differs from that of chloroform, for it has been concluded that the heart reaches anæsthetic equilibrium with a cyclopropane atmosphere soon after the areas of sensory co-ordination of the brain but more rapidly than the areas of motor co-ordination of the brain and its vital medullary centres. Thus, during light cyclopropane anæsthesia Waters (1936) showed that the heart was not affected by adrenaline injected intravenously and this indicates that the concentration of cyclopropane in the heart at this level of anæsthesia, has not rendered it susceptible to adrenaline excess. Clinical experience strengthens this view, for neither bradycardia, cardiac arrythmias nor primary cardiac failure are produced when overpressure is discretely used with cyclopropane to the level of complete sensory loss in a healthy subject; at this level of cyclopropane anæsthesia, the injection of adrenaline 1 - 200,000 for the purpose of hæmostasis, does not produce cardiovascular effects. During cyclopropane anæsthesia deeper than the level of complete sensory loss, however, adrenaline injected intravenously was shown by Waters (1936) to produce ventricular fibrillation; and the observations of Meeks, Hathaway and Orth (1937) indicate that the heart is abnormally sensitive to the effects of adrenaline at comparable levels of cyclopropane anæsthesia. In clinical anæsthetic practice, the inadvertent use of overpressure with cyclopropane at levels of anæsthesia deeper than complete sensory loss, often produces cardiac arrythmias in healthy subjects. Hence, it can be assumed at levels of cyclopropane anæsthesia deeper than complete sensory loss that the heart is in fact in anæsthetic equilibrium with the anæsthetic atmosphere. It therefore follows that the use of overpressure with cyclopropane is a dangerous procedure, and at levels of cyclopropane anæsthesia deeper than complete sensory loss overpressure must inevitably be followed by cardiac arrythmias which may end in ventricular fibrillation: for cyclopropane is poorly soluble in whole blood, and alterations in its partial pressure in the anæsthetic atmosphere are immediately reflected in its concentration in blood leaving the pulmonary capillaries and in turn in the heart itself. Since induction to the

level of complete sensory loss is rapidly accomplished with cyclopropane, reflex effects are seldom encountered during cyclopropane anæsthesia; when primary cardiac failure occurs with this anæsthetic, it can be attributed to the action of cyclopropane upon the heart itself, produced by overpressure.

When, however, the cardiac reserve of the subject is impaired prior to anæsthesia, clinical experience shows that cardiac arrythmias may be produced during light cyclopropane anæsthesia, and it may well occur in the particular subject that the partial pressure of cyclopropane at which bradycardia and/or cardiac arrythmias are abolished is insufficient to maintain an efficient anæsthetic preparation. In such subjects, cyclopropane is clearly contra-indicated and it should always be abandoned as soon as it has proved itself unsuitable for the particular subject. To persist with cyclopropane in such a subject is to risk the production of ventricular fibrillation and even if this danger is avoided, such subjects will without doubt develop cardiovascular distress in the post-anæsthetic period. Cyclopropane must be considered an anæsthetic scarcely less dangerous than chloroform in inexperienced hands. It is a gas above its critical temperature, as such it is readily controllable and for this reason is a safe and a valuable anæsthetic in the hands of an experienced anæsthetist. Surgeons, however, complain of excessive general oozing which often occurs from cut surfaces during cyclopropane anæsthesia.

Trichlorethylene is an anæsthetic vapour, with a boiling point of 87 degrees Centigrade, which produces the standard sequence of anæsthetic depression when a graduated method of induction is employed. With trichlorethylene in the conditions of clinical practice, muscular relaxation cannot be achieved and attempts are invariably followed by cardiac arrythmias, which are to be looked upon as the precursors of primary cardiac failure. When death occurs during trichlorethylene anæsthesia, there is reason to believe that it must be attributed to primary cardiac failure produced by the direct action of this anæsthetic upon the heart. Evidence has been discussed which indicates that the sequence of absorption of trichlorethylene by the body—and, in consequence, the pattern of its behaviour when overpressure is used—is similar to that of cyclopropane. But its relative non-volatility, its low vapour-pressure at room temperature, and its slow diffusion rate render it

a more difficult anæsthetic to control than cyclopropane; cardiac arrythmias, once established during trichlorethylene anæsthesia, are more difficult to abolish than they are with the anæsthetic gas, cyclopropane. Ostlere (1948) excluded subjects with cardiac irregularities from the series of cases which he reviewed, and it has been concluded that trichlorethylene is best avoided when the cardiac reserve of the subject is impaired.

Trichlorethyl-alcohol which has been used rectally in basal dosage in Man, must be mentioned only to be condemned. Wood (1938) and Hewer and Belfrage (1938) have each reported a fatality with this agent; in both, death appeared to be due to primary cardiac failure. Hewer (1946) considers it to be unsuitable for use in clinical anæsthetic practice.

It can be concluded that chloroform, cyclopropane and trichlorethylene produce the standard sequence of anæsthetic depression when a graduated method of induction is employed in a healthy subject. In each instance, however, the use of over-pressure may produce primary cardiac failure by the direct action of these anæsthetics upon the heart of a healthy subject. This catastrophe is more likely in a subject whose cardiac reserve is impaired prior to anæsthesia; and in such subjects it is a wise clinical convention to avoid all three anæsthetics, for even if primary cardiac failure is evaded during anæsthesia, cardiovascular distress is likely to occur in the post-anæsthetic period. Trichlorethylene and, more especially, cyclopropane are suitable for use in clinical anæsthetic practice, for an effective concentration of these anæsthetics in the heart itself is achieved at a time in anæsthesia when reflex effects produced by emotional and physical stress are impossible. Chloroform and trichlorethyl-alcohol, however, are considered to be unsuitable in clinical anæsthetic practice, for over-pressure with these anæsthetics may depress the heart during light anæsthesia when reflex effects are possible. Deficient venous return produces the same effects with these anæsthetics as has been seen to occur with the group already discussed.

The discussion on chloroform shows that cardiac arrythmias may be produced by the direct action of this anæsthetic on the heart itself, and that they may be precipitated by reflex effects initiated by emotional and/or physical stress during light anæsthesia. When the other anæthetics in common clinical use produce

or are made to produce the standard sequence of anæsthetic response without depressing the vital medullary centres with overdose or anoxia, and when with posture and/or intravenous therapy venous return is adequate for the maintenance of an effective cardiac output, electrocardiographic recordings during anæsthesia reveal that cardiac arrythmias may occur. These arrythmias may be reflex in origin and they may be produced by the action of the anæsthetic on the heart itself. It is proposed to discuss the cause, the character, the incidence and the import of these arrythmias in clinical practice.

In normal conditions of life, the rate and the rhythm of the heart is governed by the sino-auricular node (S-A node) which is the normal pacemaker of the heart. The vagus nerve exerts a constant tonic inhibitory action on the rate of heart beat. It exerts its greatest effect upon the S-A node; the auriculo-ventricular node (A-V node) is less effected by the vagus; and when the ventricules are entirely divorced from auricular control, the idioventricular rhythm which results is not controlled by the vagus nerve. Normally, vagal control is of paramount importance in determining the rate and rhythm of the heart. Cardiac acceleration is mediated through excitor fibres from the inferior cervical and first thoracic sympathetic ganglia. When adrenaline is perfused through a denervated heart, its rate, force and output are increased Its oxygen consumption rises but is greater than can be accounted for by the increased cardiac output, and there is little doubt that adrenaline acts directly upon the special junctional tissue and on the myocardium itself, increasing their excitability and irritability. Adrenaline stimulates an intact heart in like manner, but the rise of blood-pressure which occurs usually produces reflex vagal cardiac slowing. With a sufficiently large intravenous dose of adrenaline, the rise of blood-pressure produced may cause vagal depression of the normal pacemaker with the escape of the A-V node or the bundle or the ventricular tissue; and the ventricular tachycardia, ventricular extrasystoles or ventricular fibrillation which may occur are attributed to the combined effect of the escape of lower centres of rhythmicity from the normal pacemaker and to the increased excitability and irritability of the ventricular tissue. Normally the sympathetic and parasympathetic effectors of the heart interact harmoniously to adjust the rate and rhythm of the

heart within those limits which give a cardiac output in keeping with the metabolic rate of the subject.

Evidence has been discussed which indicates that emotional control is abolished and somatic sensibility is depressed with the anæsthetic depression of the cerebral cortex during the stage of non-cooperative stupor; during this stage of anæsthesia sympathetic overaction occurs in response to emotional and physical stress. It results in a rise of pulse rate, or in sinus arrythmia, or in sinus tachycardia. Kurtz, Bennett and Shapero (1936) observed electrocardiographically that sinus arrythmia occurred in about one-quarter of subjects with all the anæsthetics in common clinical use, including procaine. Their results show that sinus irregularities were about 10 per cent. commoner with the weak anæsthetics, nitrous oxide and ethylene, than with potent anæsthetics such as cyclopropane and the ethers, which produce a deeper level of anæsthetic depression. Sinus arrythmia is regarded as a physiological variation of cardiac rhythm and can be looked upon as the natural vagal response to the rapid rhythm produced by sympathetic overaction. This is emphasised by its greater incidence during light anæsthesia with nitrous oxide or ethylene when the correcting influence of the vagus is likely to be required.

These sympathetic effects—namely, sinus tachycardia and sinus arrythmia—are rare in an adequately premedicated subject who has been induced with evipan or pentothal injected at a proper rate, if anæsthesia to the level of anæsthetic sleep is achieved with the maintenance anæsthetic before barbiturate anæsthesia has fallen below this level of anæsthetic depression. If, however, induction is slow and troublesome, or if the technique of administration permits recovery from barbiturate anæsthesia to reach the stage of non-cooperative stupor before anæsthesia with the maintenance anæsthetic has reached the stage of anæsthetic sleep, then appropriate external stimulation can produce reflex sympathetic overaction. Thus, there is reason to believe that cardiovascular reflex effects of a sympathetic nature are characteristic of the stage of non-cooperative stupor rather than of the anæsthetic used, and that these reflex effects can be abolished by a technique of induction which reduces the duration of the stage of non-cooperative stupor to an infinitesimal period of time. It is observed, too, that sinus arrythmia or sinus tachycardia during

the stage of non-cooperative stupor seldom if ever produces significant cardiovascular distress. In the absence of other factors, the pulse-rate returns to normal limits soon after the onset of anæsthetic sleep.

With the onset of anæsthetic sleep the sympathetic entities of the hypothalamus are depressed and sympathetic overaction ceases but the anterior and medial hypothalamic nuclei are still active and vagal overaction in response to appropriate stimulation can occur at this level. Since the introduction of atropine as a pre-anæsthetic medicant, cardiovascular reflex effects during the stage of anæsthetic sleep are infrequent: if they do occur, they are of the gravest import. In spite of adequate atropine, an appropriate stimulus of sufficient intensity during the stage of light anæsthetic sleep produces para-sympathetic reflex effects which may endanger the life of the subject. Vagal overaction may produce sinus bradycardia or a complete dissociation of auricular and ventricular systoles with the onset of ventricular rhythm or it may produce complete cardiac arrest. The writer has records of two cases of fatal vagal inhibition of the heart in healthy soldiers during the light anæsthetic sleep stage of di-ethyl ether anæsthesia. Similar calamities during this level of anæsthesia have been reported from time to time in current literature during operations on the prepuce, the clitoris, the vagina and the cervix, and cardiac arrythmias are twice as frequent during light anæsthesia for surgical procedures in the neck than they are in any other site. Guedel (1937) states: " If such reflex effects are to be prevented, anæsthesia must be maintained at the lower border of the first plane "—that is, at the level of deep anæsthesia sleep when the para-sympathetic entities of the hypothalamus are depressed.

When at length the stage of complete sensory loss has been attained, the subject fails to react in a reflex manner to all except the most intense forms of proprioceptive stimulus but he responds to interoceptive stimuli which react upon the chemoreceptors in the arch of the aorta and the carotid bodies, such as anoxia carbon dioxide, fall of blood pressure produced by hæmorrhage or deficient venous return, etc At the level of complete sensory loss or deeper, it is observed that the trauma associated with modern surgical procedures produces, at most, insignificant autonomic effects of minor intensity and short duration. Thus, at

this level of anæsthesia the vagus nerve can be manipulated or a carotid body tumour removed in an adequately atropinized subject without producing alterations of cardiac rhythm that are clinically appreciable. In a series of 209 human subjects, during 119 extrathoracic operations observed electrocardiographically, however, Kuntz, Bennett and Shapero (1936) found that cardiac arrythmias occurred not infrequently during surgical anæsthesia. They can be divided into two main groups, namely, arrythmias indicative of a displaced pacemaker and those which produce ectopic beats and abnormal rhythms. Table 58, constructed from the results of these observers, shows the incidence of these two types of arrythmia, together with the site of ectopic beats.

TABLE 58.

THE INCIDENCE AND THE SITE OF CARDIAC ARRYTHMIAS DURING SURGICAL ANÆSTHESIA.

(From the figures of Kuntz, Bennett and Shapero, 1936.)

Anæsthesia		Incidence of		
		Displaced Pacemaker	Extrasystoles	
With	ethylene	18%	18%	Auricular & A-V Node
	di-ethyl ether	63%	20%	Auricular & A-V Node
	procaine	8%	31%	
	nitrous oxide	60%	50%	
	cyclopropane	49%	53%	Ventricular
In	normal hearts	49%	27%	
	abnormal hearts	49%	69%	

Since at anæsthesia to the level of complete sensory loss or deeper, somatic reflex effects are abolished and autonomic reflex effects integrated at a medullary level are of short duration and insignificant intensity, these cardiac arrythmias during surgical anæsthesia are unlikely to be produced by reflex action and must be attributed to other factors. Their frequency during surgical anæsthesia and the fact that their incidence varies with different blood-borne anæsthetics as shown in Table 58 strengthens this view. Moreover, evidence has been discussed which indicates that

the stage of non-cooperative stupor seldom if ever produces significant cardiovascular distress. In the absence of other factors, the pulse-rate returns to normal limits soon after the onset of anæsthetic sleep.

With the onset of anæsthetic sleep the sympathetic entities of the hypothalamus are depressed and sympathetic overaction ceases but the anterior and medial hypothalamic nuclei are still active and vagal overaction in response to appropriate stimulation can occur at this level. Since the introduction of atropine as a pre-anæsthetic medicant, cardiovascular reflex effects during the stage of anæsthetic sleep are infrequent: if they do occur, they are of the gravest import. In spite of adequate atropine, an appropriate stimulus of sufficient intensity during the stage of light anæsthetic sleep produces para-sympathetic reflex effects which may endanger the life of the subject. Vagal overaction may produce sinus bradycardia or a complete dissociation of auricular and ventricular systoles with the onset of ventricular rhythm or it may produce complete cardiac arrest. The writer has records of two cases of fatal vagal inhibition of the heart in healthy soldiers during the light anæsthetic sleep stage of di-ethyl ether anæsthesia. Similar calamities during this level of anæsthesia have been reported from time to time in current literature during operations on the prepuce, the clitoris, the vagina and the cervix, and cardiac arrythmias are twice as frequent during light anæsthesia for surgical procedures in the neck than they are in any other site. Guedel (1937) states: " If such reflex effects are to be prevented, anæsthesia must be maintained at the lower border of the first plane "—that is, at the level of deep anæsthesia sleep when the para-sympathetic entities of the hypothalamus are depressed.

When at length the stage of complete sensory loss has been attained, the subject fails to react in a reflex manner to all except the most intense forms of proprioceptive stimulus but he responds to interoceptive stimuli which react upon the chemoreceptors in the arch of the aorta and the carotid bodies, such as anoxia, carbon dioxide, fall of blood pressure produced by hæmorrhage or deficient venous return, etc. At the level of complete sensory loss or deeper, it is observed that the trauma associated with modern surgical procedures produces, at most, insignificant autonomic effects of minor intensity and short duration. Thus, at

pacemaker, *per se*, is of little clinical significance and seldom reduces the functional efficiency of the heart as a circulatory pump.

The incidence and the site of extrasystoles during anæsthesia, as shown in Table 58, permits further inferences to be made. The high incidence of extrasystoles during nitrous oxide anæsthesia can again be attributed to the local effect of anoxia on the heart itself. If nitrous oxide is excluded and anoxia avoided, it is seen that the incidence and the site of ectopic beats bear no direct relationship to the effective concentration of the anæsthetic which it is possible to achieve in circulating blood. Table 58 shows that the incidence of extrasystoles is of the same order and they are located in the A-V node or the auricle, with the weak anæsthetic, ethylene, and with the potent anæsthetic, di-ethyl ether. They occur in one-third of cases with procaine and during local anæsthesia the blood concentration of the narcotic is low and is not an effective concentration for the brain. With cyclopropane, whose anæsthetic potency lies midway between that of ethylene and di-ethyl ether, extrasystoles occur in more than half the subjects and they are ventricular in origin. It is clear that the site and the incidence of ectopic beats during anæsthesia must be referred to the particular anæsthetic used and not directly to the depth of anæsthesia. In terms of the frequency of extrasystoles and their site of origin, the anæsthetics in common clinical use fall naturally into two broad groups. On the one hand, anæsthetics—such as ethylene and di-ethyl ether—whose oil/water partition coefficient is less than 14 produce few ectopic beats and their site is auricular. On the other, with cyclopropane, chloroform and trichlorethylene, whose oil/water partition is high, extrasystoles are frequent and their site is ventricular.

Ectopic beats and abnormal cardiac rhythms may be escape phenomena due solely to depression of the normal pacemaker; they may be due to the excitation or increased irritability of the lower centres of rhythmicity; or they may be due to the escape of excited or irritated lower centres made possible by the coincident depression of the normal pacemaker.

It can be assumed at the outset that depression of the normal pacemaker may be a factor which produces a set of circumstances favourable to the establishment of abnormal lower centres but it is

anæsthetics with a high oil/water partition coefficient may depress the heart by their direct action on this organ. And if it is accepted as a basis for discussion that the anæsthetics in common clinical use can produce irregularities of cardiac rhythm by their direct action on the heart itself, the observations of Kuntz *et al.*, shown in Table 58, indicate that cardiac arrythmias during surgical anæsthesia may be produced by the depression of the special junctional tissue of the heart or by an increased excitability or irritability of the heart or by a combination of both effects.

When the effective concentration of the anæsthetic in circulating blood is low, as in procaine and nitrous oxide anæsthesia, Table 58 shows that the pacemaker is displaced in 8 per cent. of cases with procaine and in 60 per cent. of cases with nitrous oxide anæsthesia. During nitrous oxide anæsthesia, however, relative degrees of anoxia are the rule rather than the exception and the high incidence of displacement of the pacemaker with this anæsthetic can be attributed to the effect of anoxia on the heart itself, or to vagal overaction due to light anæsthesia, rather than to the depressive action of nitrous oxide on the heart. If nitrous oxide is excluded, Table 58 shows that the incidence of a displaced pacemaker varies as the effective concentration of the anæsthetic which it is possible to achieve in circulating blood in clinical anæsthetic practice. Thus, the incidence of this type of arrythmia is lowest with procaine and increases through ethylene and cyclopropane to be greatest during di-ethyl ether anæsthesia. Hence, the incidence of displacement of the pacemaker varies as the depth of anæsthesia, and during surgical anæsthesia reflex effects are unlikely to be a significant cause of this phenomenon. It may be inferred, therefore, that this escape mechanism can be attributed to the anæsthetic depression of the special junctional tissue of the heart. There is reason to believe that the S-A node is most susceptible to the action of depressants, and then the A-V node, and that this special junctional tissue is progressively depressed as the effective concentration of the anæsthetic in circulating blood, and in turn in the heart, is increased. It is observed, too, that the presence of pathological conditions of the heart do not increase the incidence of a depressed pacemaker during anæsthesia, for this effect occurs with equal frequency in normal and in abnormal hearts. If anoxia is avoided, the anæsthetic depression of the

pacemaker, *per se*, is of little clinical significance and seldom reduces the functional efficiency of the heart as a circulatory pump.

The incidence and the site of extrasystoles during anæsthesia, as shown in Table 58, permits further inferences to be made. The high incidence of extrasystoles during nitrous oxide anæsthesia can again be attributed to the local effect of anoxia on the heart itself. If nitrous oxide is excluded and anoxia avoided, it is seen that the incidence and the site of ectopic beats bear no direct relationship to the effective concentration of the anæsthetic which it is possible to achieve in circulating blood. Table 58 shows that the incidence of extrasystoles is of the same order and they are located in the A-V node or the auricle, with the weak anæsthetic, ethylene, and with the potent anæsthetic, di-ethyl ether. They occur in one-third of cases with procaine and during local anæsthesia the blood concentration of the narcotic is low and is not an effective concentration for the brain. With cyclopropane, whose anæsthetic potency lies midway between that of ethylene and di-ethyl ether, extrasystoles occur in more than half the subjects and they are ventricular in origin. It is clear that the site and the incidence of ectopic beats during anæsthesia must be referred to the particular anæsthetic used and not directly to the depth of anæsthesia. In terms of the frequency of extrasystoles and their site of origin, the anæsthetics in common clinical use fall naturally into two broad groups. On the one hand, anæsthetics —such as ethylene and di-ethyl ether—whose oil/water partition coefficient is less than 14 produce few ectopic beats and their site is auricular. On the other, with cyclopropane, chloroform and [illegible] partition is high, extrasystoles are [illegible].

Ectopic beats and abnormal cardiac rhythms may be escape phenomena due solely to depression of the normal pacemaker; they may be due to the excitation or increased irritability of the lower centres of rhythmicity; or they may be due to the escape of excited or irritated lower centres made possible by the coincident depression of the normal pacemaker.

It can be assumed at the outset that depression of the normal pacemaker may be a factor which produces a set of circumstances favourable to the establishment of abnormal lower centres but it is

not the dominant factor in the production of these arrythmias. Thus, with di-ethyl ether the incidence of displacement of the pacemaker is high but extrasystoles are rare. They are always auricular in origin, and while nodal rhythm may occur with di-ethyl ether, it is never followed by ventricular extrasystoles or ventricular rhythms. On the other hand, displacement of the pacemaker with cyclopropane is less frequent but the incidence of extrasystoles is high. They are always ventricular in origin and are always preceded by nodal rhythm which can be produced at will in clinical anæsthetic practice by the use of overpressure. Hence, although di-ethyl ether can depress the normal pacemaker and release and/or irritate foci of abnormal rhythm in auricular tissue, it does not produce this effect below the A-V node. Cyclopropane in high blood concentrations, however, depresses the normal pacemaker with the onset of nodal rhythm, and ventricular foci of abnormal rhythm are then released and/or irritated with the production of ventricular extrasystoles or ventricular rhythms. Moreover, extrasystoles are three times as frequent in abnormal as in normal hearts. Since disease of the heart potentiates the action of anæsthetics in this respect, it is probable that these arrythmias are produced by the anæsthetic depression of the special junctional tissue and, perhaps, of the myocardium, together with the release and or the excitation of lower centres of abnormal rhythmicity.

standard dose of adrenaline was injected during chloroform anæsthesia, they observed nodal rhythm, A-V block and slow ventricular rhythm indicating displacement of the pacemaker and ventricular extrasystoles, and occasionally ventricular tachycardia which indicated irritability. During cyclopropane anæsthesia, the injection of the standard dose of adrenaline produced occasional nodal rhythm and nodal extrasystoles, ventricular extrasystoles, fast ventricular rhythms and tachycardia and—once—ventricular fibrillation. Thus [illegible] ot only [illegible] of the [illegible]

It can be concluded that di-ethyl ether does not, and cyclopropane and chloroform do, increase the irritability of centres of rhythmicity below the A-V node. Meeks *et al.* observed that the increased irritability of the lower centres of rhythmicity produced by cyclopropane and chloroform was directly related to their concentration in the anæsthetic atmosphere: and this suggests that the rate of uptake of these anæsthetics by the heart is a dominant factor in the production of these arrythmias.

Evidence has been discussed in Chapter X which indicates that the rate of uptake of di-ethyl ether by the brain is *more rapid* than its uptake by the heart. When overpressure is used with di-ethyl ether, the clinical signs of the anæsthetic depression of the brain give ample warning of impending overdose and effectively prevent the accumulation of a concentration of this anæsthetic in the heart which might produce arrythmias even in a subject with extreme myocardial degeneration. On the other hand, anæsthetics with a high oil/water partition coefficient—such as cyclopropane, chloroform and, it is presumed, trichlorethylene—are absorbed by the heart more rapidly than by the brain. On this account, and because their solubility in blood is low, a concentration of these anæsthetics can be produced in the heart when overpressure is used which will depress the normal pacemaker and increase the irritability of abnormal lower ventricular centres of rhythmicity before the signs made manifest by the anæsthetic depression of the brain give warning of impending disaster. It can be concluded that the rate of uptake of the common clinical anæsthetics by the heart is a dominant factor in the production of

cardiac arrythmias during surgical anæsthesia. Anæsthetics whose oil/water partition coefficient is more than unity and less than 14. may depress the pacemake
with this group of anæsthe
reduce the efficiency of the heart as a circulatory pump. In normal hearts, anæsthetics with a high oil/water partition coefficient not only displace the pacemaker but may also increase the *irritability of lower ventricular centres of rhythmicity. Nodal* rhythms are readily produced with overpressure and are the precursors of ventricular arrythmias which may produce grave cardiovascular embarrassment and/or fatal cardiac failure. It is difficult to escape the impression that these anæsthetics exert a specific irritating action on ventricular tissue. Insufficient is known of the physical properties of procaine and the other local anæsthetics in common clinical use to permit them to be classified accurately. They displace the pacemaker in the blood concentrations attained clinically, and the bradycardia observed during high spinal anæsthesia will be recognised as nodal rhythm. According to the figures shown in Table 58 procaine produces extrasystoles more frequently than di-ethyl ether and less often than cyclo-*propane; Long et al. (1949) have produced fatal ventricular* arrythmias in dogs by the intravenous administration of procaine. The pattern of behaviour of local anæsthetics suggests a greater similarity to the anæsthetics with a high oil/water partition coefficient; and until their physical properties have been thoroughly investigated, it is a wise convention to class them as relatively innocuous members of this group. Finally, a sense of proportion is maintained when it is realised that the cardiac arrythmias produced by anæsthetics whose oil/water partition coefficient is high and which can be excreted from the heart rapidly (such as cyclopropane) can invariably be ablated if the partial pressure of the anæsthetic in the atmosphere breathed is reduced to zero and/or if di-ethyl is substituted for it. In like manner the arrythmias which occur during local anæsthesia are abolished if di-ethyl ether is administered

co-relate the alterations of cardiac rhythm and signs of cardiovascular distress which are manifest to the anæsthetist during clinical anæsthesia with the arrythmias revealed electrocardiographically. During clinical anæsthesia, the pulse may be fast, slow or irregular; alterations of blood pressure may occur; and signs of anoxia, of a stagnant circulation and of venous engorgement are readily recognised. The whole trend of this discussion indicates, however, that the significance of some at least of these clinical signs differs not only at different levels of anæsthetic depression but also as between anæsthetics with an oil/water partition coefficient of more than unity and less than 14 (such as di-ethyl ether) and those anæsthetics (such as cyclopropane and trichlorethylene) whose oil/water partition coefficient is high. For simplicity of description the import of cardiac arrythmias during anæsthesia are discussed in respect to each group, di-ethyl ether being taken as representative of the first group and cyclopropane as typical of the second group of anæsthetics.

During di-ethyl ether anæsthesia, the heart-rate may increase during the non-cooperative stupor stage of induction; it may increase when anoxia is present, when venous return is allowed to reach a critically low level and, occasionally, when depression of the pacemaker produces fast nodal rhythm and/or auricular extrasystoles.

When emotional and/or physical stress is permitted to act during a long drawn-out di-ethyl ether induction, the heart-rate may increase to 120 beats and more per minute; in children in whom vagal control is not yet fully established the heart-rate may be considerably faster. This increase is a sinus effect produced by sympathetic overaction; when sympathetic overaction ceases with the onset of anæsthetic sleep, the arrest of the excessive secretion of adrenaline, the rapid oxidation of the adrenaline which has been released and vagal action soon reduces the heart-rate to normal limits These sinus effects can be prevented or reduced to minimal proportions by adequate premedication followed by a swift and trouble-free induction to the level of anæsthetic sleep. A rise of heart-rate of this origin seldom if ever produces significant alterations of the functional activity of the heart.

At any stage of di-ethyl ether anæsthesia, anoxia of a degree corresponding to Wiggers' first or second stage produces a rise of

cardiac arrythmias during surgical anæsthesia. Anæsthetics whose oil/water partition coefficient is more than unity and less than 14 may depress the pacemaker and produce auricular arrythmias; and with this group of anæsthetics these arrythmias do not significantly reduce the efficiency of the heart as a circulatory pump. In normal hearts, anæsthetics with a high oil/water partition coefficient not only displace the pacemaker but may also increase the irritability of lower ventricular centres of rhythmicity. Nodal rhythms are readily produced with overpressure and are the precursors of ventricular arrythmias which may produce grave cardiovascular embarrassment and/or fatal cardiac failure. It is difficult to escape the impression that these anæsthetics exert a specific irritating action on ventricular tissue. Insufficient is known of the physical properties of procaine and the other local anæsthetics in common clinical use to permit them to be classified accurately. They displace the pacemaker in the blood concentrations attained clinically, and the bradycardia observed during high spinal anæsthesia will be recognised as nodal rhythm. According to the figures shown in Table 58 procaine produces extrasystoles more frequently than di-ethyl ether and less often than cyclopropane; Long *et al* (1949) have produced fatal ventricular arrythmias in dogs by the intravenous administration of procaine. The pattern of behaviour of local anæsthetics suggests a greater similarity to the anæsthetics with a high oil/water partition coefficient; and until their physical properties have been thoroughly investigated, it is a wise convention to class them as relatively innocuous members of this group. Finally, a sense of proportion is maintained when it is realised that the cardiac arrythmias produced by anæsthetics whose oil/water partition coefficient is high and which can be excreted from the heart rapidly (such as cyclopropane) can invariably be ablated if the partial pressure of the anæsthetic in the atmosphere breathed is reduced to zero and/or if di-ethyl is substituted for it. In like manner the arrythmias which occur during local anæsthesia are abolished if di-ethyl ether is administered

The electrocardiograph, however, is an exceedingly sensitive instrument; during anæsthesia only about one-twelfth of the cases in which it reveals a cardiac arrythmia show clinical evidence of cardiac irregularities. It is therefore important to attempt to

of complete sensory loss or deeper, and in neither case was it possible to make an electrocardiographic record. In the first case which was presumed to be a slow nodal rhythm, the heart-rate was 52 beats per minute; venous return was adequate for an effective cardiac output and the blood pressure did not fall; oxygenation was readily maintained throughout and there was no suggestion of circulatory embarrassment. It was abolished as anæsthesia lightened. The second case was thought to be a slow nodal rhythm complicated with slight anoxia. The heart-rate was observed to be 50 beats per minute with extrasystoles; the blood pressure did not fall significantly and oxygenation appeared to be adequate but within about one minute of its onset, oxygen insufflation rapidly abolished the extrasystoles and the heart rate rapidly rose to 76 beats per minute.

If a swift and trouble-free induction to the level of complete sensory loss is achieved with di-ethyl ether and anoxia and deficient venous return are avoided throughout, significant cardiovascular embarrassment is a rare event in clinical anæsthetic practice. In an adequately oxygenated subject, the tachycardia produced by emotional and/or physical stress during a long drawn-out induction, or by fast nodal rhythm during anæsthetic maintenance, seldom if ever produces cardiovascular distress. A rise of pulse-rate produced by anoxia and/or by deficient venous return is of serious import. Unless relieved, tachycardia of this origin rapidly causes cardiovascular distress and may result in cardiac arrest. Bradycardia should always be viewed with anxious expectation. Vagal overaction during the stage of anæsthetic sleep may slow the pulse, and in response to appropriate external stimulation of adequate intensity may even produce cardiac arrest. During di-ethyl ether anæsthesia maintained at the level of complete sensory loss or deeper, a slow pulse indicates a slow nodal rhythm which, *per se*, seldom produces cardiovascular embarrassment. If however anoxia and/or deficient venous return is allowed to act when a slow nodal rhythm is present, auricular extrasystoles may occur and this set of circumstances is thought to indicate impending cardiovascular distress. It has been observed that these extrasystoles disappear when anoxia and/or deficient venous return is relieved.

The evidence reviewed suggests that when anoxia and deficient

pulse-rate and in the absence of other factors the heart-rate rapidly returns to normal limits when the oxygen lack is relieved. If anoxia persists, however, the subject soon passes to Wiggers' third stage of anoxia and ST-segment and T-wave abnormalities followed by bundle branch block or complete A-V dissociation appear and are soon followed by cardiac arrest.

If anoxia is avoided and di-ethyl anæsthesia to the level of complete sensory loss or deeper abolishes the reflex response to external stimulation, a rise of pulse-rate is almost always due to deficient venous return produced by prolonged muscular relaxation, hæmorrhage or surgical shock; it returns to normal when whole blood is administered intravenously at a proper rate. If deficient venous return is not corrected, however, the cardiac output falls and the vicious circle of fall of blood pressure and anoxia soon results in cardiac arrest.

In an adequately oxygenated subject maintained with di-ethyl ether at the level of complete sensory loss or deeper, in whom venous return is adequate for an effective cardiac output, cardiac arrythmias are uncommon. When they do occur they take the form of depression of the pacemaker with—as a rule—a fast nodal rhythm and/or auricular extrasystoles. These effects are more likely to occur during di-ethyl anæsthesia in toxic subjects and in subjects with heart disease. In the absence of anoxia and deficient venous return, although they are a source of anxiety, they seldom reduce the cardiac output to a level which leads to the dangers of congestive heart failure or peripheral vascular effects which may result in thrombosis It is probable that such effects occur with di-ethyl ether only when the heart-rate exceeds 180 - 200 for several hours or more. These fast nodal rhythms and auricular extrasystoles can usually be abolished by reducing the level of anæsthetic depression to that of complete sensory loss, and—since the introduction of d-tubo-curarine chloride—this is the greatest level of anæsthetic depression desired or required in clinical anæsthetic practice

A slow pulse during di-ethyl ether anæsthesia is a rare event Vagal overaction during the stage of anæsthetic sleep can occur in response to appropriate external stimulation and can result in a slow pulse and/or cardiac arrest The writer has only twice observed bradycardia during di-ethyl ether anæsthesia at the level

cause of these ventricular arrythmias. A rising pulse-rate during anæsthetic maintenance with cyclopropane may be due to anoxia, to deficient venous return, to sinus effects produced by too light anæsthesia, or to a fast nodal rhythm which is the precursor of ventricular arrythmias. Anoxia should be rapidly abolished by assisted respiration and deficient venous return corrected by the intravenous administration of whole blood at a proper rate. If tachycardia persists, it is now due either to sinus effects produced by too light anæsthesia or to a fast nodal rhythm produced by too great a partial pressure of cyclopropane in the anæsthetic atmosphere, and it may be difficult to determine the factor which is acting. When in doubt, it is a wise convention to replace cyclopropane *with di-ethyl ether and commence assisted respiration.* In this instance, if the tachycardia is due to light anæsthesia laryngeal effects may decide the issue and anæsthesia can be quickly deepened with cyclopropane; whereas if fast nodal rhythm is the real factor, di-ethyl ether will abolish the effect without alteration in the level of anæsthetic depression.

Induction with trichlorethylene is not rapid, but sinus effects are nonetheless uncommon. When overpressure is inadvertently used with trichlorethylene a slow nodal rhythm produces bradycardia, and this is followed by ventricular arrythmias which may result in primary cardiac failure unless the overpressure is rapidly relieved. Bradycardia *is relieved by reducing the partial pressure* of trichlorethylene in the anæsthetic atmosphere; if irregular irregularities of rhythm appear, insufflation with an oxygen atmosphere should be begun immediately.

Anoxia and deficient venous return depress the cardiovascular system during cyclopropane and trichlorethylene anæsthesia in the same way as with members of the first group of anæsthetics. These anæsthetics, both with a high oil/water partition coefficient, differ from the members of the first group, for overpressure with cyclopropane and trichlorethylene directly depresses ventricular tissue and ventricular arrythmias and/or primary cardiac failure may occur. In the absence of electrocardiographic *records, modifications* of cardiac rhythm that are manifest clinically with these anæsthetics of the second group can be attributed to their direct action on the heart itself; and in the interest of safety they should

venous return are avoided vagal overaction during the stage of anæsthetic sleep is the only grave danger to be anticipated during di-ethyl ether anæsthesia. In modern anæsthetic practice, vagal overaction can readily be prevented by adequate premedication and a swift and trouble-free induction to the level of complete sensory loss. Ethylene and the other anæsthetics of this group behave similarly to di-ethyl ether.

Anæsthesia to the level of complete sensory loss may be achieved so rapidly with cyclopropane that autonomic overaction produced by emotional or physical stress is very rare in an adequately premedicated subject during a cyclopropane induction On this account, sinus tachycardia or sinus bradycardia are seldom seen during a cyclopropane induction in clinical practice. When bradycardia occurs with cyclopropane during anæsthetic maintenance, it can be attributed to a depressed pacemaker and a slow nodal rhythm is common when too great a partial pressure of cyclopropane is present in the anæsthetic atmosphere. Occasionally, such overpressure produces a tachycardia which can be interpreted as nodal rhythm with coincident irritation of the A-V node. As long as the pulse-rate is regular and does not fall below 70 or rise above about 110 beats per minute, it can be assumed that the partial pressure of cyclopropane in the anæsthetic atmosphere is below the minimum concentration necessary to depress the heart of the particular subject. Should the pulse-rate fall below 70 beats per minute during cyclopropane anæsthesia, this should be interpreted as a slow nodal rhythm, and, because depression of the pacemaker with cyclopropane may soon be followed by ventricular arrythmias which eventually produce cardiovascular distress and/or primary cardiac failure, a slow pulse *must be regarded as the fore-runner of disaster. A rate slower* than 70 beats per minute therefore calls for an immediate reduction in the partial pressure of cyclopropane in the anæsthetic atmosphere If, however, a slow pulse-rate is accompanied by irregular irregularities of rhythm, it must be assumed that the pacemaker is depressed and that lower centres of impulse formation in the ventricle are irritable. In this instance the subject is in grave danger of cardiac arrest: controlled respiration with an oxygen atmosphere should be begun, for this manoeuvre accelerates the excretion of cyclopropane from the heart itself and abolishes the

cause of these ventricular arrythmias. A rising pulse-rate during anæsthetic maintenance with cyclopropane may be due to anoxia, to deficient venous return, to sinus effects produced by too light anæsthesia, or to a fast nodal rhythm which is the precursor of ventricular arrythmias. Anoxia should be rapidly abolished by assisted respiration and deficient venous return corrected by the intravenous administration of whole blood at a proper rate. If tachycardia persists, it is now due either to sinus effects produced by too light anæsthesia or to a fast nodal rhythm produced by too great a partial pressure of cyclopropane in the anæsthetic atmosphere, and it may be difficult to determine the factor which is acting. When in doubt, it is a wise convention to replace cyclopropane with di-ethyl ether and commence assisted respiration In this instance, if the tachycardia is due to light anæsthesia laryngeal effects may decide the issue and anæsthesia can be quickly deepened with cyclopropane; whereas if fast nodal rhythm is the real factor, di-ethyl ether will abolish the effect without alteration in the level of anæsthetic depression

Induction with trichlorethylene is not rapid, but sinus effects are nonetheless uncommon. When overpressure is inadvertently used with trichlorethylene a slow nodal rhythm produces bradycardia, and this is followed by ventricular arrythmias which may result in primary cardiac failure unless the overpressure is rapidly relieved. Bradycardia is relieved by reducing the partial pressure of trichlorethylene in the anæsthetic atmosphere; if irregular irregularities of rhythm appear, insufflation with an oxygen atmosphere should be begun immediately.

Anoxia and deficient venous return depress the cardiovascular system during cyclopropane and trichlorethylene anæsthesia in the same way as with members of the first group of anæsthetics. These anæsthetics, both with a high oil/water partition coefficient, differ from the members of the first group, for overpressure with cyclopropane and trichlorethylene directly depresses ventricular tissue and ventricular arrythmias and/or primary cardiac failure may occur. In the absence of electrocardiographic records, modifications of cardiac rhythm that are manifest clinically with these anæsthetics of the second group can be attributed to their direct action on the heart itself; and in the interest of safety they should

be interpreted as the precursors — or the actual presence — of ventricular involvement.

Theines *et al.* (1941) believe that the anæsthetic agent used is more important in the production of cardiac arrythmias than is the type of operative procedure. If reflex effects are abolished by the maintenance of a sufficient level of anæsthetic depression and deficient venous return is prevented, the evidence set out in this discussion tends to confirm this opinion. Recently, however, surgical interference on the heart has become a commonplace event and to the effects of anæsthetisia on the cardiovascular system must be added, in cardiac surgery, the problem of operative trauma to the heart itself.

The anæsthetic problems arising during surgical interference for the relief of congenital or acquired heart disease with cyanosis have not yet crystallized. In such subjects, the avoidance of anæsthetics which may directly depress the already embarrassed cardiovascular system appears evidently desirable, and is the more imperative because this type of surgery introduces the additional factor of direct significant interference with the heart itself. Ziegler (1948) points out that thoracotomy and mediastinal dissection interrupts the collateral circulation which is present in such subjects and may further reduce the already pathologically low tension of oxygen in arterial blood. To this is added the premeditated collapse of the left lung which is necessary for an efficient surgical exposure, and the quiet intermittent artificial insufflation of the right lung which is often necessary in the interest of a placid surgical field. Finally, the character of the congenital cardiac abnormality for which the subject seeks relief may make it impossible to raise appreciably the oxygen tension of arterial blood by assisted or controlled respiration with an oxygen atmosphere. Two of the writer's colleagues, Dr. Rink and Dr Hutton, are of the opinion that the intelligent use of intravenous procaine appreciably diminishes the irritability of the heart during direct surgical interference on the heart itself. There can be little doubt that the penultimate signs of cardiac arrest—namely, significant changes in the rate and character of the heart-beat combined with a fall of blood pressure, a progressive decrease in the oxygen saturation of arterial blood and the mechanical dilatation of the heart—are manifestations of myocardial depression which

eventually results from anoxia, produced by an inadequate oxygen content in blood flowing in the coronary circulation.

Further information of the problems and hazards of anæsthesia during this very specialized type of surgery are to be found in the works of Rink *et al.* (1948) and Ziegler (1948).

When direct surgical trauma on the heart is excluded, it can be concluded that primary cardiac failure during anæsthesia may be produced by reflex effects which may occur during too light anæsthesia, and by the direct action on the heart which may occur when overpressure is used with anæsthetics having too high an oil/water partition coefficient. With all the other anæsthetics in common clinical use, cardiac arrest during anæsthesia takes the form of secondary cardiac failure, produced by anæsthetic overdose and when anoxia or deficient venous return is undetected or ignored

The Kidneys. The most striking result of blood-borne anæsthesia on the kidneys is the reduction in the volume of urine secreted. Evidence has been discussed indicating that the volume of urine secreted during anæsthesia varies as the level of anæsthetic depression of the central nervous system. Thus, nitrous oxide, which can produce anæsthesia only to the level of anæsthetic sleep, has no more effect upon urinary secretion than has natural sleep of corresponding intensity. Moreover when anæsthesia to the level of anæsthetic sleep is produced with the other blood-borne anæsthetics in common clinical use, the volume of urine secreted during anæsthesia corresponds to that produced during nitrous oxide anæsthesia or natural sleep. Ethylene, which can produce anæsthesia only to the level of complete sensory loss, materially reduces the volume of urine secreted; and when this level of anæsthetic depression of the central nervous system is produced with the other blood-borne anæsthetics in common clinical use, the volume of urine secreted corresponds to that produced during ethylene anæsthesia to this level of anæsthetic depression. When the level of anæsthetic depression of the central nervous system is greater than complete sensory loss, urinary secretion is to all intent and purpose completely suppressed. This effect is produced with the ethers, chloroform, cyclopropane, ethyl chloride, the barbiturates and in fact with all the common clinical blood-borne anæsthetics capable of producing anæsthesia deeper than complete

sensory loss. Table 53 shows how urinary secretion is progressively suppressed as di-ethyl anæsthesia gradually deepens. And it *can be concluded that the reduction of urinary secretion varies as* the level of anæsthetic depression, and is not determined by the type of blood-borne anæsthetic employed.

MacNider (1920) observed fatal anuria in dogs after chloroform and di-ethyl ether anæsthesia. In Man, after chloroform and all the other anæsthetics in common clinical use, post-anæsthetic anuria does not occur and the water retention produced during surgical anæsthesia is freely reversible; for, as anæsthesia lightens, urinary secretion increases in volume and in the post-anæsthetic period a compensatory diuresis frequently occurs. In the writer's experience and in that of surgical colleagues at St. Peter's Hospital for Stone, anuria in the post-anæsthetic period which could be attributed to the anæsthetic employed does not occur in Man. Moreover, when pathological conditions of the kidney are present prior to anæsthesia, *in the absence of anoxia and other* occasional factors, an exacerbation of the pre-existing renal condition sufficient to nullify the beneficial effect of surgical interference has seldom been observed. Unless the anæsthetic used possessed a deleterious side-action which specifically affected the kidneys, this is to be expected; for, like the liver, the physiological reserve of the kidneys is very considerable. Thus, when three-*quarters of the kidney substance is removed, recovery occurs on* a normal diet; but, on a high protein diet, the blood nitrogen rises, albuminuria occurs, the volume of urine secreted increases and blood dilution occurs. If both kidneys are removed or become functionless owing to obstruction in the renal tubules or the ureters, uræmia develops and death of the subject occurs within five to seven days Hence, it can be inferred that the complete suppression of urinary secretion produced by blood-borne anæsthesia, lasting even for five to seven hours, can have little deleterious effect upon the subject if this suppression of urine is freely reversible when anæsthesia ceases. In clinical practice, the depression of renal function produced during anæsthesia is freely reversible and renal damage seldom occurs, but it is equally clear that errors or accidents of anæsthetic administration and other occasional factors may produce renal damage.

The presence of casts and albumin in the urine in the post-anæsthetic period is diagnostic of renal damage. Stephens (1929) stated that albuminuria occurred in about 20 per cent. of cases after chloroform anæsthesia. Hogan (1915) observed casts and albumin in the urine in 26 per cent. of cases of di-ethyl ether, and Stephens reported that albuminuria practically always occurred after the prolonged administration of di-ethyl ether. One cannot query these results in the case of chloroform, for this drug is known to cause protoplasmic degeneration of the kidneys; at St. Peter's Hospital for Stone, when chloroform was in common clinical use, it was thought that open di-ethyl ether was less harmful to the kidneys than was chloroform. These results, however, do not coincide with those observed in modern anæsthetic practice. Thus, in a series of 119 consecutive anæsthetics in adequately oxygenated subjects whose age was between twenty and forty years, casts were not observed in the first post-anæsthetic specimen of urine. In 109 of these subjects whose urine was normal prior to anæsthesia only four had albumin in the first post-anæsthetic specimen of urine. It was observed in two of the forty-five subjects who had nitrous oxide, oxygen and di-ethyl ether and in two of the forty-one spinal anæsthetics, but none of the twenty-three minor surgical cases to whom pentothal was administered had albumin in the first post-anæsthetic specimen of urine. Of the remaining ten cases of the series who had albuminuria prior to anæsthesia, neither the three who had nitrous oxide, oxygen and di-ethyl ether nor the seven who had spinal anæsthesia, showed an exacerbation of their albuminuria in the first post-anæsthetic specimen of urine. Hence, in this series of 119 adequately oxygenated subjects, anæsthesia did not produce casts, it did not produce a significant exacerbation of albuminuria in those subjects whose kidneys were diseased prior to anæsthesia, and albuminuria occurred in the first post-anæsthetic specimen of urine in 3 6 per cent. of the normal subjects. The relatively low age group of the subjects of this series may have favoured this result but in the main, it coincides with the results obtained in genito-urinary subjects between fifty and seventy years of age

The commonest cause of albuminuria in the post-anæsthetic period is anoxia during anæsthetic maintenance. Normal glomerular epithelia hold back plasma proteins but the permeability

sensory loss. Table 53 shows how urinary secretion is progressively suppressed as di-ethyl anæsthesia gradually deepens. And it can be concluded that the reduction of urinary secretion varies as the level of anæsthetic depression, and is not determined by the type of blood-borne anæsthetic employed.

MacNider (1920) observed fatal anuria in dogs after chloroform and di-ethyl ether anæsthesia. In Man, after chloroform and all the other anæsthetics in common clinical use, post-anæsthetic anuria does not occur and the water retention produced during surgical anæsthesia is freely reversible; for, as anæsthesia lightens, urinary secretion increases in volume and in the post-anæsthetic period a compensatory diuresis frequently occurs. In the writer's experience and in that of surgical colleagues at St. Peter's Hospital for Stone, anuria in the post-anæsthetic period which could be attributed to the anæsthetic employed does not occur in Man. Moreover, when pathological conditions of the kidney are present prior to anæsthesia, in the absence of anoxia and other occasional factors, an exacerbation of the pre-existing renal condition sufficient to nullify the beneficial effect of surgical interference has seldom been observed Unless the anæsthetic used possessed a deleterious side-action which specifically affected the kidneys, this is to be expected; for, like the liver, the physiological reserve of the kidneys is very considerable. Thus, when three-quarters of the kidney substance is removed, recovery occurs on a normal diet, but, on a high protein diet, the blood nitrogen rises, albuminuria occurs, the volume of urine secreted increases and blood dilution occurs. If both kidneys are removed or become functionless owing to obstruction in the renal tubules or the ureters, uræmia develops and death of the subject occurs within five to seven days. Hence, it can be inferred that the complete suppression of urinary secretion produced by blood-borne anæsthesia, lasting even for five to seven hours, can have little deleterious effect upon the subject if this suppression of urine is freely reversible when anæsthesia ceases. In clinical practice, the depression of renal function produced during anæsthesia is freely reversible and renal damage seldom occurs, but it is equally clear that errors or accidents of anæsthetic administration and other occasional factors may produce renal damage.

that renal damage may occur in Man. Since the introduction of d-tubo-curarine chloride as a muscle relaxant, an efficient anæsthetic preparation can be maintained for a very long time with blood-borne anæsthesia to the level of complete sensory loss and adequate curarization. At this level of anæsthesia the alkali reserve of the body is not significantly reduced, and renal damage is seldom observed in the post-anæsthetic period. And when these several occasional factors are avoided during clinical anæsthesia, significant renal damage is seldom if ever observed after anæsthesia with all the anæsthetics in common clinical use, except perhaps chloroform. The ability of the kidneys to concentrate urinary urea within the first twenty-four hours of the cessation of anæsthesia, as shown in Table 53, strengthens this conclusion; for after a period of oliguria due to pathological causes, it takes much longer for the kidneys to regain the ability to concentrate urinary urea than for the blood urea to become normal.

No explanation has been advanced for the progressive diminution of urinary secretion during anæsthesia. In the absence of these occasional factors it is not due to renal damage, and to speculation on its cause is interesting.

The data in Table 27 show that the uptake of blood-borne anæsthetics by the kidneys is rapid, but during clinical anæsthesia the concentration of the anæsthetic in glands and in the kidneys and organs, other than the brain, is insufficient to depress their functional activity During uncomplicated anæsthesia the minute-volume of renal blood flow is reduced in keeping with the diminution of metabolic rate that occurs: but renal blood flow, providing it is adequate, is a relatively unimportant factor in determining the volume of urine secreted. Wright (1942) states that 55 - 90 per cent. of the glomeruli of a rabbit's kidney are patent during anæsthesia, if this applies in Man, there can be little if any reduction in the volume of filtrate which reaches the renal tubules from Bowman's capsule during anæsthesia. Since the volume of urine reaching the renal pelvis *via* the collecting tubules is reduced during anæsthetic sleep and is to all intent and purpose completely suppressed during anæsthesia to the level of complete sensory loss or deeper, it can be assumed that the re-absorption of this glomerular filtrate in the renal tubules is increased during anæsthetic sleep and is almost complete at deeper levels of anæsthesia.

of the glomerular membrane is increased by the anoxia produced by asphyxia and circulatory failure and by toxins. When anoxia occurs, serum albumin and—in severe or prolonged anoxia—serum globulin pass through the glomerular filter and appear in the urine. When asphyxial damage to the glomerular membrane is severe, red blood corpuscles also pass through the filter and enter the glomeruli, as the fluid is filtered out, the glomeruli become blocked with a mass of erythrocytes. In consequence, blood-flow through the glomeruli is completely arrested; moreover, the engorged renal veins within the kidney substance press on the collecting tubules, and the flow of urine is arrested.

Oliguria and even anuria can be produced by an incompatible blood transfusion. When erythrocytes of an incompatible group are injected intravenously, these red blood corpuscles are agglutinated and may occlude capillaries in different parts of the body where they undergo hæmolysis. The hæmoglobin released is broken down, in part to form bilirubin which results in jaundice, while the remainder passes through the glomerular filter to be precipitated in the renal tubules as acid hæmatin which blocks the tubules and obstructs the flow of urine. In severe cases, complete anuria develops and the subject dies of uræmia in from eight to 10 days Renal tubules may also become blocked by crystals during sulphonamide therapy and the tubular epithelium undergoes hyaline degeneration which may go on to necrosis and desquamation. In this instance, fluids leak back freely from the damaged tubules into the peri-tubular blood vessels. This leakage of fluid and/or its more complete re-absorption from the renal tubules may also occur in surgical shock, after the crush syndrome,

that renal damage may occur in Man. Since the introduction of d-tubo-curarine chloride as a muscle relaxant, an efficient anæsthetic preparation can be maintained for a very long time with blood-borne anæsthesia to the level of complete sensory loss and adequate curarization. At this level of anæsthesia the alkali reserve of the body is not significantly reduced, and renal damage is seldom observed in the post-anæsthetic period. And when these several occasional factors are avoided during clinical anæsthesia, significant renal damage is seldom if ever observed after anæsthesia with all the anæsthetics in common clinical use, except perhaps chloroform. The ability of the kidneys to concentrate urinary urea within the first twenty-four hours of the cessation of anæsthesia, as shown in Table 53, strengthens this conclusion; for after a period of oliguria due to pathological causes, it takes much longer for the kidneys to regain the ability to concentrate urinary urea than for the blood urea to become normal

No explanation has been advanced for the progressive diminution of urinary secretion during anæsthesia. In the absence of these occasional factors it is not due to renal damage, and to speculation on its cause is interesting.

The data in Table 27 show that the uptake of blood-borne anæsthetics by the kidneys is rapid; but during clinical anæsthesia the concentration of the anæsthetic in glands and in the kidneys and organs, other than the brain, is insufficient to depress their functional activity During uncomplicated anæsthesia the minute-volume of renal blood flow is reduced in keeping with the diminution of metabolic rate that occurs but renal blood flow, providing it is adequate, is a relatively unimportant factor in determining the volume of urine secreted. Wright (1942) states that 55 - 90 per cent. of the glomeruli of a rabbit's kidney are patent during anæsthesia; if this applies in Man, there can be little if any reduction in the volume of filtrate which reaches the renal tubules from Bowman's capsule during anæsthesia. Since the volume of urine reaching the renal pelvis *via* the collecting tubules is reduced during anæsthetic sleep and is to all intent and purpose completely suppressed during anæsthesia to the level of *complete* sensory loss or deeper, it can be assumed that the re-absorption of this glomerular filtrate in the renal tubules is increased during anæsthetic sleep and is almost complete at deeper levels of anæsthesia.

This mechanism is probably responsible for the retention, not only of water but also of other threshold substances; for despite the inevitable rise of blood-sugar during anæsthesia, glycosuria is a rare event in the first post-anæsthetic specimen of urine (except in an unbalanced diabetic). Excessive re-absorption in the renal tubules during anæsthesia could be attributed to an increased permeability produced by the local action of the blood-borne anæsthetic; but the freely reversible character of this effect, and the lack of renal damage in the post-anæsthetic period, make it improbable that blood-borne anæsthetics exercise a local action on the renal tubules. It could be explained by the release of antidiuretic hormone from the posterior pituitary increasing as anæsthesia deepens.

When anæsthetizing a subject for an investigation of renal function, a swift and trouble-free induction to the level of complete sensory loss is achieved with pentothal, cyclopropane and oxygen; and when the catheterizing cystoscope has been passed and the ureteric catheters introduced, it is found that urinary secretion is to all intent and purpose completely suppressed at this level of anæsthetic depression. If, however, a switch is made to nitrous oxide and oxygen as soon as the cystoscope is *in situ* anæsthetic recovery rapidly proceeds to the level of anæsthetic sleep and urinary secretion, as shown by the rate of flow from the ureteric catheters, is copious enough not to delay the collection of urinary specimens. It seems significant that in anæsthesia to the level of complete sensory loss, the anterior and medial hypothalamic nuclei—and, it is presumed, the supra-optic nuclei which control the release of anti-diuretic hormone from the posterior lobe of the pituitary—are completely depressed. During the stage of anæsthetic sleep and during natural sleep, the depression of this group of nuclei is not complete, urinary secretion is materially reduced and in each instance this reduction of urinary secretion is of the same order. Pickford (1947) injected ACh into the supra-optic nuclei of dogs and her work can be interpreted as suggesting that the stimulation of these nuclei inhibits the release of anti-diuretic hormone. It suggests that the depression of these nuclei during anæsthesia and natural sleep results in an increased release of anti-diuretic hormone, and offers an explanation for the freely reversible water-retention which occurs during anæsthesia.

Evidence has been discussed which indicates that (with the possible exception of chloroform) the anæsthetics in common clinical use do not produce significant renal damage during a properly conducted anæsthetic. There is little doubt that errors and accidents during anæsthetic administration may produce renal damage of varying degrees of intensity. The cause of the diminished urinary secretion which occurs during natural sleep and during anæsthesia is not known, but this effect is freely reversible and does not produce renal damage. Data have been discussed suggesting that the diminished urinary secretion is produced by increased re-absorption in the renal tubules. This effect could be attributed to an increased release of anti-diuretic hormone, and an attempt has been made to rationalize the mechanism of the release of anti-diuretic hormone during natural sleep and during anæsthesia.

The Suprarenal Glands. Experimental and clinical evidence has been discussed which indicates that sympathetic overaction and, in turn, excessive secretion of adrenaline may occur during the non-cooperative stupor stage of anæsthesia. It can be reduced to minimal proportions by adequate premedication and a swift and trouble-free induction; and when the sympathetic entities of the hypothalamus are depressed with the onset of anæsthetic sleep, the secretion of adrenaline falls to the basal level. At the level of anæsthetic sleep or deeper, it can be concluded that the secretion of the adrenal glands is depressed in keeping with the metabolic rate of the subject.

The Pancreas. The pancreas is a dual organ: pancreatic juice is secreted in the alveolar tissue and discharges into the second part of the duodenum, and the islets of Langerhans form an internal secretion—insulin—which is released into the blood stream. Zucker *et al* (1931) observed that the blood amylase increased during anæsthesia and returned to normal within twenty-four hours of the cessation of anæsthesia. A rise of blood amylase occurs when the discharge of pancreatic juice is mechanically obstructed; this observation may be explained by the continued secretion of pancreatic juice at a basal level during anæsthesia with inadequate discharge of this secretion into the duodenum.

It has been concluded that the secretion of insulin is reduced in keeping with the metabolic rate during anæsthesia, and no evidence

This mechanism is probably responsible for the retention, not only of water but also of other threshold substances; for despite the inevitable rise of blood-sugar during anæsthesia, glycosuria is a rare event in the first post-anæsthetic specimen of urine (except in an unbalanced diabetic). Excessive re-absorption in the renal tubules during anæsthesia could be attributed to an increased permeability produced by the local action of the blood-borne anæsthetic; but the freely reversible character of this effect, and the lack of renal damage in the post-anæsthetic period, make it improbable that blood-borne anæsthetics exercise a local action on the renal tubules. It could be explained by the release of antidiuretic hormone from the posterior pituitary increasing as anæsthesia deepens.

When anæsthetizing a subject for an investigation of renal function, a swift and trouble-free induction to the level of complete sensory loss is achieved with pentothal, cyclopropane and oxygen; and when the catheterizing cystoscope has been passed and the ureteric catheters introduced, it is found that urinary secretion is to all intent and purpose completely suppressed at this level of anæsthetic depression. If, however, a switch is made to nitrous oxide and oxygen as soon as the cystoscope is *in situ* anæsthetic recovery rapidly proceeds to the level of anæsthetic sleep and urinary secretion, as shown by the rate of flow from the ureteric catheters, is copious enough not to delay the collection of urinary specimens It seems significant that in anæsthesia to the level of complete sensory loss, the anterior and medial hypothalamic nuclei—and, it is presumed, the supra-optic nuclei which control the release of anti-diuretic hormone from the posterior lobe of the pituitary—are completely depressed. During the stage of anæsthetic sleep and during natural sleep, the depression of this group of nuclei is not complete; urinary secretion is materially reduced and in each instance this reduction of urinary secretion is of the same order. Pickford (1947) injected ACh into the supra-optic nuclei of dogs and her work can be interpreted as suggesting that the stimulation of these nuclei inhibits the release of anti-diuretic hormone. It suggests that the depression of these nuclei during anæsthesia and natural sleep results in an increased release of anti-diuretic hormone, and offers an explanation for the freely reversible water-retention which occurs during anæsthesia

death can occur from fulminating delayed chloroform poisoning without obvious jaundice. When the bilirubin content of blood serum rises above its normal value of 0·1 to 0·5 mg. per cent., jaundice occurs. In mammals, bilirubin is formed by the destruction of red blood corpuscles, mainly in the reticulo-endothelial system of the spleen and bone marrow. The liver plays only a minor role in its formation and is concerned mainly with the excretion of bilirubin. When the parenchyma of the liver is damaged, experimental and clinical observations indicate that the excretion of bilirubin is one of the first functions to fail, and it is rare for jaundice to be absent in delayed chloroform poisoning. The onset of jaundice may be delayed, for the accumulation of bilirubin in blood serum depends not only on the inability of the liver to excrete bile pigment, but also on the rate of its formation by the reticulo-endothelial system of the body.

Coma, which is a constant feature of delayed chloroform poisoning, is usually preceded by a drowsy irritable condition with slow cerebration. On the third or fourth day, coma is deep, but the cough and swallow reflexes are usually present up to a few hours before death. At this stage liver tenderness may also be present, and there may be signs of cerebral irritation, with restlessness, fine muscular twitching or generalized clonic movements During the last twenty-four hours of life, the body temperature rises and may reach 103 degrees Fahrenheit just before the death of the subject, which occurs from one to twelve days after the administration of the anæsthetic.

At autopsy, the blood (which is fluid) stains endothelium, and the organs are bile-stained Hæmorrhages are often present in the peritoneum, the upper gastro-intestinal tract and other organs. Fatty degeneration is to be found in the pancreas and the heart. The kidneys show epithelial degeneration and the spleen is usually enlarged. During pregnancy the placenta often separates and necrosis of the placenta with hæmorrhage is present. The liver is flabby and diminished in bulk, there is wrinkling of the capsule, which strips easily. Sometimes, on the contrary, the liver is enlarged, with a tense capsule. On section, the parenchyma of the liver is very soft, the cut surface has a yellowish appearance; and when more than three to five days have elapsed between the administration of the anæsthetic and the death of the subject,

has been advanced to suggest that the residual rise of blood sugar during anæsthesia has anything to do with a diminished secretion of insulin. It has been seen that a rise of blood sugar, a rise of blood fats, a rise of blood acetone bodies, and a ketosis in keeping with the level of anæsthetic depression occurs during all types of anæsthesia; this sequence of events simulates the metabolic upset which occurs during diabetes mellitus. The upset of carbohydrate metabolism which occurs during anæsthesia causes a slight transitory exacerbation of symptoms in a balanced diabetic, but in an unbalanced diabetic intense and serious sequelæ may follow the administration of an anæsthetic. When diabetes mellitus is present it is imperative to have the subject balanced by medical treatment prior to anæsthesia, and premedication should include a balanced dose of insulin and glucose. It is usual to give such a subject 15 units of insulin with 30 grams of glucose five hours before the commencement of anæsthetic induction, but it is wise to be guided in respect of dosage by the physician in charge of the case.

The Liver. In the absence of anoxia, only two of the anæsthetics in common clinical use (namely, chloroform and di-vinyl ether) may produce histological changes in liver tissue with symptoms of hepatitis. This condition, described by Guthrie in 1894 and known as delayed chloroform poisoning, is an acute diffuse necrosis of the liver. It is a rare sequela of chloroform or di-vinyl ether anæsthesia, but starvation prior to anæsthesia and anoxia during anæsthetic maintenance predispose to its occurrence, when delayed chloroform poisoning is established, recovery is rare. The symptoms of delayed chloroform poisoning appear between twenty-four and forty-eight hours after anæsthesia ceases; they consist of vomiting, jaundice, coma, and, as death approaches, the body temperature rises, and there may be muscular twitching and, perhaps, generalized convulsions

When irreversible liver damage occurs during chloroform anæsthesia there is, after the immediate post-anæsthetic vomiting has ceased, a latent period of twenty-four to forty-eight hours during which the subject appears to be perfectly well. Vomiting then recommences, and it is the copious coffee-ground vomitus of a dilated stomach, for atonic dilatation of the stomach, rather than vomiting, is a constant feature of delayed chloroform poisoning Jaundice usually appears shortly after the onset of vomiting, but

glycogen is rapidly regained, and glycogenosis proceeds rapidly if glucose is supplied to the subject in the post-anæsthetic period.

When delayed chloroform poisoning follows chloroform anæsthesia, the glucose content of blood in the post-anæsthetic period is low, but the intravenous use of glucose in the treatment of this condition confuses the results of blood sugar analysis. However, Stander (1924) reported a blood sugar of 0·088 per cent. in delayed chloroform poisoning which rose to 0·182 per cent. after intravenous glucose therapy; and Gibberd (1935) reported a blood sugar of 0·093 per cent. on the fifth day after glucose had been given intravenously. Although it is impossible to say whether the liver regains the ability to store glycogen and convert lactic acid into liver glycogen during the latent period of delayed chloroform poisoning, there is little doubt that, when this condition is established, hypoglycæmia and a raised blood lactic acid occur. When to this is added the decreased levulose and galactose tolerance, it can be assumed that the ability of the liver to store glycogen, to transform lactic acid into liver glycogen and to convert other sugars into an easily assimilated form is lost early in delayed chloroform poisoning.

With the exhaustion of the glycogen content of the liver, the body calls first on fats and then on proteins as sources of energy. As dépot fats, *élément variable*, are mobilized, there is a rise of blood fats, and fatty infiltration of the liver occurs. Lipæmia has been observed early in delayed chloroform poisoning. Whipple and Sperry (1909) observed fatty infiltration of the liver in dogs six to ten hours after the cessation of chloroform anæsthesia and they state that this change reached its maximum effect in about twenty-four hours after chloroform anæsthesia ceased. This early mobilization of fats in delayed chloroform poisoning confirms the early failure of carbohydrate metabolism and suggests that normal glycogenesis is not regained in such subjects when anæsthesia ceases

It has been concluded that protein metabolism is maintained at its resting level during anæsthetic maintenance, but there is a retention of the waste products of protein metabolism during anæsthesia and to a lesser degree during the immediate post-anæsthetic period, due to the diminished secretion of urine. The

discrete reddish patches scattered evenly throughout the yellowish liver substance are observed. Histological examination shows that the liver necrosis of delayed chloroform poisoning follows a definite pattern, for it is intense at the centre of each lobule and spreads peripherally. This central necrosis is not influenced by the blood supply, for Whipple and Sperry (1909) showed that it occurred when the hepatic artery was ligated and when the portal blood supply was excluded by an Ech fistula. Necrosis is extensive throughout the whole liver substance, which is converted into a mass of amorphous débris lying amongst the portal tracts with a few peripheral cells to show that necrosis started at the centre of the lobule.

After death from delayed chloroform poisoning, the post-mortem appearances indicate that an acute diffuse necrosis of the liver is the dominant factor responsible for death. This necrosis progressively destroys the liver tissue and, in turn, the functional activity of its contained cells. The physiological reserve of the liver is very great and the biochemical changes which occur during delayed chloroform poisoning are therefore not identical with those produced by the surgical extirpation of the liver.

All the anæsthetics in common clinical use, including chloroform and di-vinyl ether, modify the carbohydrate metabolism of the body in an identical manner during anæsthesia. A purposeful hyperglycæmia in keeping with the depth of anæsthesia is accompanied by a corresponding depletion of liver glycogen. This is followed, when liver glycogen has fallen to a certain critically low level, by an attempt to utilize muscle glycogen as a source of glucose Evidence has been discussed which indicates that during deep anæsthesia the liver does not readily transform lactic acid into liver glycogen to be subsequently released as glucose, and the lactic acid content of blood rises as anæsthesia proceeds When liver glycogen has been depleted by starvation prior to anæsthesia, the purposeful hyperglycæmia is not so intense as in normal subjects maintained at a comparable depth of anæsthesia, and the call on muscle glycogen as a source of glucose occurs earlier in anæsthesia. Normal anæsthetic recovery is characterised by the rapid return of blood sugar to its normal resting level. The ability of the liver to store glucose as glycogen and to convert lactic acid into liver

glycogen is rapidly regained, and glycogenosis proceeds rapidly if glucose is supplied to the subject in the post-anæsthetic period.

When delayed chloroform poisoning follows chloroform anæsthesia, the glucose content of blood in the post-anæsthetic period is low, but the intravenous use of glucose in the treatment of this condition confuses the results of blood sugar analysis. However, Stander (1924) reported a blood sugar of 0·088 per cent. in delayed chloroform poisoning which rose to 0·182 per cent. after intravenous glucose therapy; and Gibberd (1935) reported a blood sugar of 0·093 per cent. on the fifth day after glucose had been given intravenously. Although it is impossible to say whether the liver regains the ability to store glycogen and convert lactic acid into liver glycogen during the latent period of delayed chloroform poisoning, there is little doubt that, when this condition is established, hypoglycæmia and a raised blood lactic acid occur. When to this is added the decreased levulose and galactose tolerance, it can be assumed that the ability of the liver to store glycogen, to transform lactic acid into liver glycogen and to convert other sugars into an easily assimilated form is lost early in delayed chloroform poisoning.

With the exhaustion of the glycogen content of the liver, the body calls first on fats and then on proteins as sources of energy. As dépot fats, *élément variable*, are mobilized, there is a rise of blood fats, and fatty infiltration of the liver occurs. Lipæmia has been observed early in delayed chloroform poisoning. Whipple and Sperry (1909) observed fatty infiltration of the liver in dogs six to ten hours after the cessation of chloroform anæsthesia and they state that this change reached its maximum effect in about twenty-four hours after chloroform anæsthesia ceased This early mobilization of fats in delayed chloroform poisoning confirms the early failure of carbohydrate metabolism and suggests that normal glycogenesis is not regained in such subjects when anæsthesia ceases.

It has been concluded that protein metabolism is maintained at its resting level during anæsthetic maintenance, but there is a retention of the waste products of protein metabolism during anæsthesia and to a lesser degree during the immediate post-anæsthetic period, due to the diminished secretion of urine. The

blood urea rises and blood amino acids fall to a corresponding degree during anæsthetic maintenance, to return to their resting levels early in the post-anæsthetic period.

Rabinowitch's case (1929) of very rapid intense acute yellow atrophy of the liver with anuria shows that in fulminating cases of liver necrosis, the ability to utilize amino acids and to form urea may be swiftly lost, for in this case, blood amino acids rose to 216 mg. per cent. and blood urea fell to zero. The onset of delayed chloroform is less rapid, and death usually occurs from the third to the twelfth day; early in the disease, the blood urea —a measure of the N.P.N. constituents of blood—progressively rises. In one of Gibberd's cases, it was 300 mg. per cent. on the fourth day and in the other it had risen to 360 mg. per cent. on the fifth day of the disease. Most observers report relatively low blood amino acid values in delayed chloroform poisoning. In Gibberd's case it was 8·2 mg. per cent. on the sixth day, and in Stander's two cases it was 12·02 and 15·5 mg per cent. It appears that in the early stages of the disease the liver can still form urea from blood amino acids and the low blood amino acid values are so accounted for. In these cases the high blood urea cannot be attributed to water retention, for although there was incontinence the estimated daily output of urine was between 20 and 40 ounces, with a urea concentration of 2 per cent. Gibberd concludes that this high blood urea was due to excessive katabolism of protein. In fatal cases, it can be inferred that urea formation fails during the later stages of the disease; when this occurs, blood amino acids should commence to rise and, in the presence of anuria, blood urea values should remain fairly stationary. This sequence of events is suggested by Gibberd's case, in which the blood urea was 198 mg. per cent. on the third day On the fourth day it had risen to 300 mg. per cent., and on the sixth day it had increased only to 303 mg per cent. An indication of increased protein katabolism is to be found in the large increase of blood uric acid and creatinine. in dogs, uric acid is no longer converted into allantoin.

There is also a progressive fall in the blood alkaline reserve In Stander's case it was 24 2 volumes per cent. on the third day, and on the day the subject died (the fourth day) it had fallen to 17 8 volumes per cent. It has been seen that lactic acid

accumulates during delayed chloroform poisoning and the incomplete combustion of fats and excessive protein katabolism suggests the excessive formation of acetone bodies. Gibberd concludes that ketones are not present in the urine in about half the cases of delayed chloroform poisoning occurring in obstetric practice; and it is significant that ketosis occurs in the early, but not in the late stages of starvation and phosphorus poisoning. This might suggest that the ability of the liver to form acetone bodies is abolished early when the liver is damaged; but it is thought that in starvation and liver inefficiency the body can use ketones instead of carbohydrates as a source of energy. As in uræmia, one can only conclude that in diffuse liver necrosis the accumulation of lactic and of unknown acid metabolites produces the fall of alkaline reserve and the coma which precedes the death of the subject.

The liver is also responsible for the formation of fibrinogen; during surgical procedures plasma fibrinogen may be reduced by hæmorrhage, and it falls when hepatitis is present. When liver function is normal, plasma fibrinogen returns to its normal value in about six hours after hæmorrhage. Early in fatal delayed chloroform poisoning an irreversible fall of plasma fibrinogen occurs and is responsible for the ecchymoses observed in the peritoneum, the pancreas, the upper gastro-intestinal tract, etc., which are present at autopsy in such a subject.

The ability of the liver to excrete endogenous and exogenous substances is progressively reduced during delayed chloroform poisoning. Thus, bilirubin rapidly accumulates in the blood and is responsible for the jaundice which occurs during delayed chloroform poisoning. At first, a direct van den Bergh is obtained but as liver necrosis progressively increases, an indirect reaction becomes apparent on the third or fourth day of the disease. The rate of excretion of exogenous substances, such as bromsulphthalein, is also decreased when hepatitis is present.

Finally, during delayed chloroform poisoning, the ability of the liver to conjugate exogenous substances such as cresol, phenols and certain non-volatile anæsthetics progressively fails as necrosis proceeds. Their conjugation, which occurs in many tissues but primarily in the liver, is the mechanism employed to detoxicate these relatively harmful substances. Pelkan and

Whipple (1922) state that more than half the toxic phenols are oxidised by intestinal mucosa, body fluids and the liver parenchyma while the remainder are conjugated with sulphuric and glycuronic acid in the liver and rapidly excreted in this form by the kidneys. These observers found that slight liver injury does not significantly modify the conjugation of phenols; that extensive liver injury produced by chloroform always reduces the conjugation of phenols; and that extreme liver injury, such as occurs in delayed chloroform poisoning, reduces phenol conjugation to zero. Clinically, the detoxicating power of the liver is measured by its ability to conjugate benzoic acid with glycine to form hippuric acid, which is excreted in the urine.

Delayed chloroform poisoning presents a picture suggesting that normal glycogenesis is not regained in the post-anæsthetic period, and that the metabolism of fat and protein is deficient and becomes more defective as necrosis proceeds. At the same time as the power to excrete exogenous and endogenous degradation products fails, the ability to detoxicate noxious substances is lost, and the formation of fibrinogen ceases. Gibberd points out that vomiting, jaundice and coma, accompanied by identical biochemical changes, may occur in the acute yellow atrophy which on rare occasions complicates a toxæmia of pregnancy, *e g.* eclampsia, or which may occur in puerperal infection, *e g* severe hæmolytic streptococcal infection or severe B. coli infection. In such cases, an early rise of temperature and pulse rate suggests that infection is the causative agent, but in severe B. coli infection, there may be no significant rise of temperature. Although these rare cases of liver necrosis may be mistaken for delayed chloroform poisoning clinically, they present no diagnostic difficulty at autopsy. There are positive signs of sepsis; liver necrosis starts not at the centre but in the periportal or mid-zonal areas of the lobule, and necrosis is not the diffuse necrosis of delayed chloroform poisoning but is patchy in distribution, and in the case of B. coli infection there are irregular patches of caseous material scattered in the liver substance. In these cases, it is difficult to assess the part played in the production of this irreversible liver damage by chloroform anæsthesia on the one hand and by pre-existing liver disease on the other. It is generally accepted that acute diffuse necrosis of the liver

occasionally follows chloroform anæsthesia in a subject without pre-existing liver disease; and there is no doubt that when chloroform is administered to a subject with liver disease, irreversible liver damage is readily precipitated.

Adriani (1946) states that di-vinyl ether anæsthesia may cause histological changes in the liver with symptoms of hepatitis, but anæsthetic opinion concerning liver damage during di-vinyl ether anæsthesia has not yet crystallized. Bourne and Sparling (1935) reported no gross change in the liver of eleven dogs after di-vinyl ether anæsthesia unless cyanosis was present and they observed no impairment of liver function in normal and starved dogs during di-vinyl ether anæsthesia when oxygenation was adequate. On the other hand, Goldschmidt *et al.* (1934) in a series of seventy-six dogs showed conclusively that prolonged di-vinyl ether anæsthesia can produce acute diffuse liver necrosis; histologically, the liver showed central lobular necrosis spreading peripherally which resembled—but was less intense than—that produced by chloroform. The duration of anæsthesia was found to be a relevant factor and the critical period in dogs lay between two and three hours.

Bourne and Sparling (1935) consider that the action of di-vinyl ether on dogs is not comparable to its effects in Man. Since the introduction of di-vinyl ether into clinical anæsthetic practice, however, six deaths from liver necrosis in the post-anæsthetic period have been reported in Man in current literature. Shipway (1935) quotes two deaths from liver necrosis at the Johns Hopkins Hospital following prolonged di-vinyl ether anæsthesia. Killian (1937) reported a death from acute yellow atrophy of the liver on the fourth day after di-vinyl ether anæsthesia and he quotes a similar death which occurred in Baetzner's clinic. Light, Ross and Fulton (1937) reported a death fourteen hours after tonsillectomy in an ill-nourished, undersized girl of seven years who had received 10 c.c. of di-vinyl ether followed by 6 ounces of di-ethyl ether, with, at one period, severe cyanosis during anæsthesia. At autopsy, fatty degeneration, with hæmorrhage and focal degeneration of the liver was found. Finally, Bourne (1935) reported an obstetric case dying on the fifth day of an acute hepatitis after

Whipple (1922) state that more than half the toxic phenols are oxidised by intestinal mucosa, body fluids and the liver parenchyma while the remainder are conjugated with sulphuric and glycuronic acid in the liver and rapidly excreted in this form by the kidneys. These observers found that slight liver injury does not significantly modify the conjugation of phenols; that extensive liver injury produced by chloroform always reduces the conjugation of phenols; and that extreme liver injury, such as occurs in delayed chloroform poisoning, reduces phenol conjugation to zero. Clinically, the detoxicating power of the liver is measured by its ability to conjugate benzoic acid with glycine to form hippuric acid, which is excreted in the urine.

Delayed chloroform poisoning presents a picture suggesting that normal glycogenesis is not regained in the post-anæsthetic period, and that the metabolism of fat and protein is deficient and becomes more defective as necrosis proceeds. At the same time as the power to excrete exogenous and endogenous degradation products fails, the ability to detoxicate noxious substances is lost, and the formation of fibrinogen ceases. Gibberd points out that vomiting, jaundice and coma, accompanied by identical biochemical changes, may occur in the acute yellow atrophy which on rare occasions complicates a toxæmia of pregnancy, e g. eclampsia, or which may occur in puerperal infection, *e.g.* severe hæmolytic streptococcal infection or severe B. coli infection. In such cases, an early rise of temperature and pulse rate suggests that infection is the causative agent; but in severe B coli infection, there may be no significant rise of temperature. Although these rare cases of liver necrosis may be mistaken for delayed chloroform poisoning clinically, they present no diagnostic difficulty at autopsy There are positive signs of sepsis; liver necrosis starts not at the centre but in the periportal or mid-zonal areas of the lobule, and necrosis is not the diffuse necrosis of delayed chloroform poisoning but is patchy in distribution, and in the case of B. coli infection there are irregular patches of caseous material scattered in the liver substance. In these cases, it is difficult to assess the part played in the production of this irreversible liver damage by chloroform anæsthesia on the one hand and by pre-existing liver disease on the other. It is generally accepted that acute diffuse necrosis of the liver

well have produced evidence of liver injury, Goldschmidt *et. al.* (1937) used di-vinyl ether and observed no evidence of liver injury as determined by serum bilirubin estimations in the post-anæsthetic period. Ravidin *et al.* (1937) reported no liver necrosis in 2675 di-vinyl ether anæsthetics with three deaths within a week of anæsthesia, but they avoided using this anæsthetic in subjects with known hepatic derangement, and they believe that liver necrosis may occur after prolonged di-vinyl ether anæsthesia when anoxæmia is avoided throughout.

When chloroform was commonly used in clinical anæsthetic practice, acute diffuse liver necrosis was fortunately a comparatively rare event; the incidence of liver necrosis after di-vinyl ether anæsthesia is even less frequent. It can be said that the majority of subjects anæsthetised with these two anæsthetics escape irreversible liver damage and it is pertinent to ascertain the factors which predispose to acute diffuse necrosis of the liver, when chloroform or di-vinyl ether are used.

In 1908, Hunter condemned the custom of starving the subject prior to chloroform anæsthesia. Children are particularly prone to develop delayed chloroform poisoning. In a series of 662 children, Frew (1911) observed that 61·7 per cent. had acetonuria within twelve hours of admission to hospital and that acetone bodies rapidly disappeared with the administration of glucose. Since 1915, pregnant women account for a large proportion of the reported cases of delayed chloroform poisoning: the toxæmias of pregnancy, relative starvation during a long labour, and the relatively common use of chloroform in domiciliary midwifery during this period might well combine to produce this result. It was thought moreover that repeated administrations of chloroform, such as might well occur during a long and difficult labour, were more likely than one administration to produce delayed chloroform poisoning, and Gilliatt's review (1928) tends to support this contention. The observations of Goldschmidt *et al* (1934) at length confirmed what had long been suspected, namely that starvation was a predisposing factor in the production of acute diffuse necrosis in the liver. Table 59, constructed from their results, shows that liver necrosis in dogs is more than three times as frequent after chloroform than after di-vinyl ether anæsthesia and that starvation prior to anæsthesia doubled the incidence of acute

forty minutes of di-vinyl ether anæsthesia. The details of this case, as quoted by Bourne, were as follows:

> " A primipara, aged 23, due March 19th, 1935, was admitted to the hospital on February 27th, in indifferent labour. Pregnancy had been apparently normal throughout. Labour progressed normally and the patient was delivered spontaneously of a living child. Vinyl ether was given *for forty minutes*. Some thirty hours later a jaundice developed which increased daily. Analysis of the blood showed rapidly increasing urea, uric acid, non-protein nitrogen and the van den Bergh reaction indirect. Urinary output dropped to practically zero; the patient became first restless and then comatose, the jaundice deepened; blood transfusions and injections of saline and dextrose intravenously seemed to do no more than prolong life After five days of illness she died. The last figures of chemical analysis of the blood were. urea 1 75, urea nitrogen 140, uric acid 21 4, creatinine 11 0, amino acids 18 1, and the van den Bergh indirect reaction was 30 units Post-mortem examination was refused, but a small piece of liver was obtained through an abdominal incision. The specimen consisted of two pieces of liver the size of lima beans, yellowish green with red punctate markings. Section showed a hæmorrhagic necrosis of the parenchyma which started about the periportal spaces and invaded a zone of the lobule varying from 3 to 6 cells deep in this area The remaining parenchyma showed some fatty metamorphosis The picture agreed with that encountered in eclampsia "

The clinical symptoms and the biochemical findings in this case are typical of delayed chloroform poisoning. The pathological evidence, however, leads to the conclusion that eclampsia produced the liver necrosis which was the cause of the death of the subject. This case typifies the difficulty of assessing the relative influence of pre-existing liver disease and the anæsthetic employed, in producing the liver necrosis which killed the subject The pathological evidence led Bourne to conclude that di-vinyl ether was not the cause of this irreversible liver damage and he is of the opinion that the same result would have been obtained with di-ethyl ether Killian could not say whether liver damage was present prior to di-vinyl ether anæsthesia in his case and he concludes that the anæsthetic may have aggravated a pre-existing liver condition. The John Hopkins' cases were prolonged, one has no information of Baetzner's case and the case of Light *et al* was ill-nourished In subjects in whom repeated anæsthesia might

diffuse liver necrosis in each instance. It is also significant that they were unable to produce liver necrosis with di-ethyl ether even in starved animals. Goldschmidt *et al.* (1937) also showed that a high carbohydrate diet prior to anæsthesia, or excess of oxygen during anæsthesia, reduced the incidence of liver damage in chloroform and di-vinyl ether anæsthesia. During chloroform anæsthesia, an equal measure of protection was afforded by a high liver glycogen content and by excess of oxygen during anæsthesia. A high liver glycogen content produced a greater measure of protection during di-vinyl ether than during chloroform anæsthesia. A high liver glycogen content gave greater protection than excess of oxygen during di-vinyl ether anæsthesia. These results indicate that depletion of liver glycogen prior to anæsthesia, and anoxia during anæsthesia, predispose to liver necrosis when chloroform or di-vinyl ether is employed

Whipple (1938, 1942) demonstrated that protein depletion is also a predisposing cause of liver necrosis. He showed that the liver is an important site in the production of plasma protein, and wholly responsible for the formation of fibrinogen. In normal dogs an excessive depletion of plasma protein and fibrinogen can be replaced within a few hours, but the replacement of plasma protein and fibrinogen is not possible if the liver is damaged or if it is excluded by an Eck fistula. Miller and Whipple (1940) observed that normal, healthy, well-fed dogs tolerate an hour of chloroform anæsthesia to the level of muscular relaxation quite well and show little evidence of liver injury in the post-anæsthetic period, but the same exposure to chloroform produces delayed chloroform poisoning in dogs who have been starved for three days prior to anæsthesia. They observed too that dogs whose plasma protein had been reduced from the normal 6·0 to about 4 per cent. (3 5 per cent. being above the œdema level) were more sensitive to chloroform than normal dogs. Thus, six protein-depleted dogs were starved for twenty-four hours and then given chloroform for 15 to 45 minutes. On the following day, jaundice was marked and the blood fibrinogen had fallen from about 300 mg. per cent to 129 - 30 mgs. per cent. All six dogs died within the next three days and in each instance liver necrosis involving 50 to 90 per cent. of the cells of the liver was observed. A seventh protein-depleted dog was given a meal of lean steak and starved on the following

TABLE 59

THE INFLUENCE OF FEEDING ON THE INCIDENCE OF LIVER NECROSIS IN THE POST-ANÆSTHETIC PERIOD.

(*Goldschmidt* et al., *1934*)

Anæsthetic	Well Fed			Starved for 5 days		
	No of Dogs	No. of cases of liver necrosis	%	No. of Dogs	No. of cases of liver necrosis	%
Di-vinyl ether	69	13	19	7	3	43
Chloroform	13	9	69	5	5	100
Di-ethyl ether	20	0	0	8	0	0

and the N : S ratio rises; but when methionine is administered to a protein-depleted dog, the N : S ratio falls to that of a normal dog. It is known that the function of glutathione and a number of enzymes is intimately associated with the presence of -SH groups and certain halogenated compounds conjugate very readily with -SH groups. Miller *et al.* suggest that liver necrosis may result from the conjugation of chloroform with the -SH groups of glutathione and vital enzyme systems, but when the number of -SH groups is in excess of current requirements, liver damage will be avoided. If this is in fact so, it might also explain the fatty change and central necrosis that are characteristic of delayed chloroform poisoning. The intense reduction of blood when it has reached the centre of liver lobules observed by Wright (1949), and the observation of Blalock and Mason (1936) that venous blood from the liver contains considerably less oxygen than venous blood from other organs, combine to suggest that the number of free sulphydryl groups is greatest at the periphery and gradually decreases to be least at the centre of liver lobules: the reverse would obtain for disulphide groups. In this instance, central necrosis in protein-depleted dogs during chloroform anæsthesia would be a probable event. Oxygen lack pre-disposes to liver necrosis during chloroform and di-vinyl ether anæsthesia, and to minor degrees of liver damage with all other anæsthetics; and the excessive glycogenolysis produced by anoxia and the correspondingly more intense reduction of blood when it has reached the centre of liver lobules might well account for this result.

Miller and Whipple (1940) state that there is every reason to believe that human beings react (to chloroform) like dogs. The evidence discussed suggests that this is in fact so, not only for chloroform, but also for di-vinyl ether. It has been seen that irreversible liver damage can occur in animals and in Man during chloroform and di-vinyl ether anæsthesia, and that it takes the form of an acute diffuse necrosis of the liver which can be detected histologically between six and twelve hours of the cessation of anæsthesia The biochemical changes indicate that failure of the glycogen function of the liver is a precipitating cause of liver necrosis Thus, hypoglycæmia early in the post-anæsthetic period, lipæmia coupled with histological signs of fatty infiltration of the liver within six hours of the cessation of anæsthesia, and early

day; on the third day, a chloroform anæsthetic of corresponding intensity and duration was administered. This single protein meal protected the liver, for this dog did not die and its blood fibrinogen was 590 mg. per cent. and it had no jaundice on the day following the chloroform anæsthetic. Miller, Ross and Whipple (1940) showed that an even greater measure of protection from delayed chloroform poisoning was afforded by the administration of the sulphur-containing amino acids to protein-depleted dogs. Cystine was more effective than protein or plasma, and methionine gave greater protection than cystine, while amino acids which do not contain sulphur fail to protect against delayed chloroform poisoning. Their results are shown in Table 60.

These results show conclusively that protein depletion is the primary cause of acute diffuse necrosis of the liver after chloroform anæsthesia and it must be inferred that the effectiveness of carbohydrates *in protecting the liver is due to their sparing* action on the proteins at source. They also show that the administration of sulphur-containing amino acids prior to lethal chloroform anæsthesia protects from liver damage. Cystine added to a low protein diet protects protein-depleted dogs from chloroform anæsthesia of a duration sufficient to kill unprotected animals, but cystine supplements greater than a few grams often cause jaundice; and it is known that cystine under conditions of low protein intake will cause a considerable fatty infiltration of the liver. In spite of this cystine-produced jaundice before anæsthesia, protein-depleted dogs are seen to have survived a lethal chloroform anæsthetic; and, on the basis of their clinical condition and their blood fibrinogen values in the post-anæsthetic period, Miller *et al.* consider that liver damage was not very severe in these dogs. Methionine however, is shown to confer absolute protection against lethal chloroform anæsthesia It was shown, moreover, that methionine administered to a protein-depleted dog within four hours of the cessation of a lethal chloroform anæsthetic prevented liver necrosis—indicating that the liver damage produced during chloroform anæsthesia is reversible within this period of time if the sulphur-containing amino acid, methionine, is administered

The protection afforded to protein-depleted dogs by methionine during chloroform anæsthesia is in accord with the facts that the liver loses more sulphur than nitrogen during protein depletion

evidence of protein katabolism all combine to suggest depletion of liver glycogen to a critically low level during anæsthesia and inhibition of the glycogenic function of the liver early in the post-anæsthetic period, with, in consequence, the abnormal metabolism of fat and protein as a source of energy. And, in protein-depleted subjects excessive glycogenolysis caused by emotional and physical stress during anæsthetic induction, by deep and prolonged chloroform or di-vinyl ether anæsthesia, and by anoxia, produces an early demand on tissue protein—particularly that of the liver—which cannot be adequately met in such subjects. The rise of the N : S ratio of the liver in protein-depletion and the striking results of methionine therapy indicate, in the case of chloroform, that in the absence of free -SH groups chloroform produces irreversible liver damage. We have no hint of the way in which di-vinyl ether produces irreversible liver damage, but as in chloroform so in di-vinyl ether anæsthesia, a high carbohydrate diet prior to anæsthesia and excess of oxygen during anæsthetic maintenance protect from irreversible liver damage. Miller and Whipple state: " In our opinion, it would be folly to subject to short chloroform anæsthesia human patients who have been vomiting for long periods or who are in a state of inanition due to diet or infection." And it would be a wise convention to adopt the same clinical outlook with di-vinyl ether.

But excessive glycogenolysis does not produce acute liver necrosis in normal or protein-depleted subjects with di-ethyl ether or the other anæsthetics in common clinical use; and it can be concluded that liver necrosis is produced by a deleterious side-action peculiar to chloroform and di-vinyl ether which is permitted to act when the glycogen content of the liver falls below a certain critically low level in a protein-depleted subject.

Relative to the irreversible liver damage that can be produced in protein- and glycogen-depleted subjects by chloroform and di-vinyl ether, the liver damage produced by the other anæsthetics in common clinical use is trivial, and—what is more important—freely reversible. Thus, Goldschmidt *et al.* (1934) could not produce irreversible liver damage in starved dogs with di-ethyl ether; and neither di-ethyl ether nor pentothal produces irreversible liver damage in subjects with active amœbiasis of the liver if anoxia is avoided. A number of biochemical tests have been

TABLE 60.

PROTEIN, CYSTINE AND METHIONINE PROTECTION AGAINST CHLOROFORM POISONING.

(Miller, Ross and Whipple, 1940.)

Dog No.	Low Protein diet (Weeks)	Preliminary treatment	Duration of anæsthesia (minutes)	Plasma protein level (mg. per 100 c.c.)	Fibrinogen		Clinical condition
					Before Chloroform (mg per 100 c.c.)	48 hours after chloroform (mg per 100 c.c.)	
39-20	9	None	20	5 17	373	63[1]	Dead 40 hours
39-16	6	Lean beef	20	4 6-5 3	—	—	Normal
38-299	6	Lean beef	20	4·5-5·3	—	—	Normal
38-241	8	Plasma protein	20	5 2-6 3	—	352	Slight intox.
38-241	15	Plasma protein	20	4·7	370	205	Slight intox.
39-16	7	l-cystine	25	4·2	177	129	Slight intox.
38-169	6	l-cystine	27	5·0	235	260	Normal
38-340	12	l-cystine	30	5 0	223	160[1]	Moderate intox.
38-340	15	l-cystine	40	5 2	351	648	Dead 4 days
38-338	6	l-cystine	20	4·7	355	195	Slight intox.
38-338	13	l-cystine	40	4·6	237	166	Dead 4 days
39-157	9	dl-methionine	40	4 9	450	421	Normal
39-157	13	None	15	4·8	327	38[1]	Dead 36 hours
39-12	6	dl-methionine	40	4·5	264	222	Normal
39-12	10	None	15	4·5	347	44	Dead 47 hours
39-164	4	dl-methionine	40	4·2	332	401	Normal
39-164	7	Amino acids[2]	20	3 9	368	50	Severe intox.
39-130	11	dl-methionine	40	5·3	478	419	Normal
39-130	14	Amino acids[3]	20	4·8	375	165[1]	Dead 40 hours
39-10	7	None	10	5·1	387	130	Moderate intox.
39-10	10	dl-methionine	40	5·1	402	343	Slight intox.

[1] Twenty-four hours after chloroform.
[2] l-tyrosine, l-histidine, l-alanine, l-glutamic acid.
[3] [illegible]

liver disease is absent, they occur only when irreversible liver damage has been produced with chloroform or di-vinyl ether.

As has been seen, controlled glycogenolysis and an inability to convert lactic acid into liver glycogen occur during anæsthesia: evidence has been discussed indicating that the intensity of this effect varies as the depth and duration of anæsthesia and not as the particular anæsthetic agent employed. Except when irreversible liver damage is produced with chloroform or with di-vinyl ether, the glycogenic function of the liver is quickly regained when anæsthesia ceases. Neither the glucose nor the galactose tolerance tests in the post-anæsthetic period provides reliable evidence of liver function, for the absorption of these sugars from the gut may be delayed and urinary secretion is often reduced in the post-operative period. King and Aitkin (1940) suggested that the intravenous injection of galactose eliminates the error produced by sluggish absorption; but Carter and Thompson (1949) state that such a test cannot detect minor degrees of liver damage.

Because of the great reserve capacity of the liver, its ability to deaminate amino acids and to convert the ammonia so produced into urea fails only in extensive liver degeneration such as acute yellow atrophy or delayed chloroform poisoning. In clinical anæsthetic practice, the level of anæsthetic depression required for upper abdominal surgery does not affect urea formation: in such a case blood amino acids fall, while blood urea—in the presence of the diminished urinary secretion produced by this level of anæsthesia—rises in a corresponding degree. The work of Whipple and his associates has shown that plasma fibrinogen is materially lowered in the presence of severe liver damage, but the absence of significant change of plasma fibrinogen in minor degrees of liver damage makes this test useless in the early diagnosis of post-anæsthetic liver damage Adriani (1946) states that the coagulation of the blood is slightly prolonged during chloroform anæsthesia, no change occurs with cyclopropane, and it is shortened during di-ethyl ether, ethylene, avertin and nitrous oxide anæsthesia The prothrombin time is prolonged after chloroform anæsthesia, but the other anæsthetics in common clinical use do not reduce the prothrombin time. Adriani concludes that tests of liver efficiency based upon the coagulation of the blood have not yielded data of practical significance. The ability

used in an effort to assess the degree of liver damage produced by these several anæsthetics, but each type of test is concerned with only one of the many essential functions of the liver and its value depends upon the manner of its interpretation.

Bourne and others used the bromsulphalein test, which is a measure of the liver's ability to excrete exogenous substances, as a test of liver function in the post-anæsthetic period. If anoxia was present during anæsthesia, it was observed that the rate of excretion of bromsulphalein was retarded in the post-anæsthetic period with all the anæsthetics in common clinical use. In fully oxygenated subjects, chloroform anæsthesia produced impaired excretion of the dye in dogs for as long as eight days and di-ethyl ether retarded its excretion for about twenty-four hours. No retardation of its excretion was observed with di-vinyl ether, nitrous oxide, ethylene, cyclopropane, the barbiturates, paraldehyde, avertin or morphia, if anoxia was avoided throughout. Coleman (1938) observed no change in the rate of excretion of bromsulphalein with local anæsthesia, but with spinal anæsthesia the rate of excretion of the dye was retarded in 50 per cent. of cases. In spinal anæsthesia, a diminished circulatory rate must bear considerable responsibility for this effect and this factor is also a relevant one when deep blood-borne anæsthesia is maintained for a long period of time

Molitor (1941) observed that bile secretion was depressed with all the anæsthetics in common clinical use if anoxia is present, but it is significant that bile secretion in fully oxygenated subjects was depressed only during chloroform anæsthesia.

The most obvious clinical sign that may result from liver damage is jaundice. In obstructive jaundice, bilirubin accumulates in blood in significant amounts, and a direct van den Bergh reaction is obtained. In hæmolytic or in toxic jaundice, however, an indirect or delayed van den Bergh reaction occurs in the absence of biliary obstruction. In the absence of pre-existing liver disease, the bilirubin content of the blood in the post-anæsthetic period may be taken as an index of the ability of the liver to excrete endogenous substances. But jaundice, or a rise in the bilirubin content of blood or urine in the post-anæsthetic period is a very rare occurrence in clinical anæsthetic practice; when pre-existing

it is sufficiently severe to be recognised clinically. They do show that reversible liver damage of a minor character may be produced with all the anæsthetics in common clinical use when oxygen lack occurs during anæsthesia; moreover, it is difficult to escape the impression that minor degrees of liver disfunction may occur in adequately oxygenated subjects with all the common anæsthetics. This supports the view that minor degrees of protein katabolism may be a constant feature of anæsthesia; if this is in fact so, the metabolic upset in the post-anæsthetic period can be attributed in part to ketosis and in part to minor degrees of liver disfunction. In this instance, factors such as starvation and other forms of protein depletion prior to anæsthesia can be expected to increase protein katabolism during anæsthesia and, in turn, the degree of liver disfunction and metabolic upset in the post-anæsthetic period. On the other hand, glucose prior to anæsthesia and adequate oxygenation during anæsthetic maintenance have long been recognised as valuable means of reducing the metabolic upset in the post-anæsthetic period; and if the action of glucose in this respect is attributed to its protein-saving property this in turn imples protein katabolism during anæsthesia. There can be little doubt that protein depletion is a dominant factor in precipitating liver damage during chloroform and di-vinyl ether anæsthesia. And one is led to the as yet unconfirmed opinion that protein depletion prior to anæsthesia also plays a significant part in determining the intensity of reversible liver disfunction that may result when anæsthetics other than chloroform and di-vinyl ether are employed in clinical anæsthetic practice. When pathological conditions of the liver are absent prior to anæsthesia, acute diffuse liver necrosis may occur in carbohydrate- and protein-depleted subjects when chloroform or di-vinyl ether is employed. In such subjects there is also reason to believe that minor reversible degrees of liver disfunction can occur with all the other anæsthetics in common clinical use In each instance, anoxia intensifies the extent of liver damage and there is reason to believe that the degree of liver disfunction in the post-anæsthetic period is reduced to minimal proportions if carbohydrate and protein depletion is corrected prior to anæsthesia.

When, however, pathological conditions of the liver are present prior to anæsthesia, chloroform or di-vinyl ether should not be

of the liver to synthetize plasma protein appears to be affected relatively early in liver disease. Higgins *et al.* (1944) have claimed that there is a close relation between the fall of plasma albumin and the extent of liver damage; but so many factors may modify plasma albumin during anæsthesia and in the post-anæsthetic period that this test is unlikely to be of practical value. In the absence of biliary obstruction, a low plasma prothrombin indicates deficient prothrombin formation due to liver damage. The rapid return of the prothrombin level to normal when vitamin K is injected indicates that the liver is not severely damaged while severe liver damage is suggested by the failure of plasma prothrombin to respond to parenteral injection of vitamin K. This test may be of value in determining the presence or absence of minor degrees of liver damage in the post-anæsthetic period.

The capacity of the liver to conjugate benzoic acid with glycine to form hippuric acid, which is then excreted in the urine, is the best-known test of the liver's ability to detoxicate harmful substances that may have entered the blood stream; Bryan (1925) found that the synthesis of hippuric acid was markedly affected by liver damage. Schmidt *et al* (1942) observed that the detoxication of benzoic acid was reduced by 35 per cent. after di-ethyl ether anæsthesia and returned to normal within seven days. Avertin reduced the detoxication of benzoic acid by 5 - 30 per cent., and morphia and amytal in hypnotic doses produced no change. Boyce (1941) reported diminished detoxication of benzoic acid after di-ethyl ether and ethylene anæsthesia. He also reported diminished detoxication of this reagent in half the spinal anæsthetics observed, but Schmidt *et al* reported no change during spinal anæsthesia unless anoxia, hypotension or a diminished circulatory rate was permitted to occur during spinal anæsthesia. These occasional factors and the fact that hippuric acid is excreted by the kidneys account for the conflicting results In general, the hippuric acid test is often disappointing, and too much reliance should not be placed upon it in the post-anæsthetic period, for the upset of water balance and extrarenal fluid loss may produce unreliable results

These data indicate that no single test of liver function can as yet replace clinical observation in the post-anæsthetic period, for these tests seldom give reliable information of liver damage until

experience suggests and Harris and MacMartin (1944) observed that inefficient detoxication of reactive substances was frequently associated with the tropical diseases common to the Far East. Table 61 records sixteen cases suffering from various tropical

TABLE 61.
THE RATE OF EXCRETION OF HIPPURIC ACID.
(Harris and MacMartin.)

Disease	Van den Bergh	Hippuric Acid excretion. Calc. as Benzoic Acid.
†1 Amœbic abscess of liver	1·2 units	0 63 gm.
†2. Amœbic abscess of liver	0 8 units	0·28 gm.
3. Infective hepatitis	1·2 units	0 44 gm.
4. Infective hepatitis	—	0·43 gm.
5 Early cirrhosis of liver	—	0 34 gm.
6. Ascites with anæmia	—	0·42 gm.
*7. Ascites, ? Banti's	1·6 units	0 27 gm.
*8 Kala azar	—	0 60 gm.
*9. Kala azar	—	0·36 gm.
*10. Enteric fever	—	0 45 gm.
11. Malignant tertian malaria	0·4 units	0·58 gm.
12 ,,	0 4 units	0 68 gm.
13. ,,	0 5 units	0 50 gm.
*14.	—	0 60 gm.
*15 Secondary anæmia, post-malarial	—	0 53 gm.
*16 Secondary anæmia, post-malarial	—	0·52 gm.
17 Chloroform by mouth	—	0 40 gm
18. Chloroform by mouth	—	0·72 gm.
19 Chloroform by mouth	—	0·76 gm.

† Seriously ill   * Severely ill.

diseases and three cases of accidental oral ingestion of chloroform. None of these subjects had jaundice, but, notwithstanding, they all exhibited a diminished ability to detoxicate reactive substances, as shown by the rate of their excretion of hippuric acid after the intravenous administration of 1·77 gm. of sodium benzoate. The lower limit of normality for this test is the excretion within one hour of 0·7 to 0 9 gm. of hippuric acid expressed as benzoic acid. Table 61 illustrates not only the association of liver inefficiency with a variety of tropical diseases but also the presence of liver inefficiency in the absence of jaundice

used, and non-volatile anæsthetics that are detoxicated wholly or in part by the liver, should be used with care and clinical discrimination; for the control of their blood concentration is difficult and sluggish and/or faulty detoxication of these reactive substances may readily lead to anæsthetic overdose. The other common volatile anæsthetics do not produce irreversible liver damage even when pathological conditions of the liver are present; on this account, and because they are excreted unchanged by the lungs, they may be safely employed in the presence of active liver disease.

A minor degree of liver disfunction is difficult to recognise prior to anæsthesia, and the response of the subject to his pre-anæsthetic medicant affords valuable evidence of its presence. The common pre-anæsthetic medicants, morphia and scopolamine, are detoxicated in part by the liver; except when very gross liver damage is present, standard single hypnotic dosage with these premedicants does not result in dangerous overdose. The response to this standard single dosage, however, produces various degrees of hypnosis which enable one to classify the particular subject as "tolerant," "normal" or "susceptible." And it can be inferred that the detoxication of these premedicants is rapid in the tolerant group and sluggish in the susceptible group In the interest of safe administration, it must be assumed that the sluggish detoxication of the pre-anæsthetic medicant will inevitably be followed by the sluggish and/or faulty detoxication of the reactive non-volatile anæsthetics, such as evipan or pentothal, and clinical experience confirms this supposition, for such subjects are in fact susceptible to these reactive barbiturates. In subjects who have proved to be susceptible to their pre-anæsthetic medicant, therefore, intravenous barbiturate induction may be withheld or used with care and clinical discrimination, and anæsthesia should be maintained with a volatile anæsthetic (such as nitrous oxide, di-ethyl ether or cyclopropane) which is excreted by the lungs and which produces, at most, only trivial degrees of liver disfunction. Such minor degrees of liver inefficiency prior to anæsthesia are not infrequently encountered in clinical anæsthetic practice in temperate climates.

In tropical zones, however, one may frequently be called upon to anæsthetize a subject with active gross liver disease. Clinical

doses of these two agents or their substitutes is essential in all subjects before anæsthesia; in nervous subjects, relatively heavy premedication is a sound prophylactic measure. It must be remembered that atropine and scopolamine are contra-indicated when glaucoma is present; morphia produces emesis in certain subjects and pethidine can then be used as a substitute.

Retching prior to anæsthesia often has an organic basis. It is a common occurrence for a subject with an irritable throat to retch as soon as too large a dental prop is inserted or other appropriate stimuli are allowed to act. The effect can be mitigated by using a smaller prop or can be eliminated by omitting the prop and/or spraying the irritable throat with a 10 per cent. cocaine solution. Vomiting may occur before anæsthesia in subjects with certain pathological conditions of the stomach, with intestinal obstruction, with biliary or renal colic, with gastric crisis of tabes dorsalis, with pancreatitis or other abdominal catastrophies, with certain cerebral conditions, with uræmia, and also during pregnancy and the cyclic vomiting of children. Even if there is no pathological cause, the subject may come to the anæsthetic room with an overloaded stomach due to inefficient nursing, or because of the character of the surgical emergency for which he seeks relief. An overloaded stomach is not uncommonly met with in obstetric practice and in those surgical emergencies—fractures, dislocations etc.—that are usually treated in the out-patient department. In each instance, the obvious remedy is a stomach wash-out before anæsthetic induction. When this is not possible, the subject should be induced on the operating table so that the Trendelenberg position can be adopted at the first hint of gastric reflex action, and anæsthetic induction should be swiftly carried to the stage of complete sensory loss, when a stomach tube should be passed and the stomach emptied

When the pre-anæsthetic preparation of the subject has been thorough and pre-anæsthetic medication is adequate, gastro-intestinal effects are conspicuous by their absence if induction with a non-irritating blood-borne anæsthetic is swiftly carried to the level of complete sensory loss; for, at this level of anæsthetic depression or deeper the secretions of the entire tract (salivary, gastric etc.) are abolished, and the musculature of the tract from the œsophagus to the rectum, fails to react to central stimuli or

The results cited in Table 61, together with clinical experience in tropical climates, indicate that liver inefficiency is commonly associated with all the common tropical diseases; that in both temperate and tropical zones, when liver inefficiency is present or is suspected, reactive non-volatile anæsthetics should be used with discrimination; and that chloroform and di-vinyl ether should be avoided. Premedication should not be heavy in such subjects; and basal narcosis is best avoided but, if it is essential, paraldehyde —which is excreted in part by the lungs—is safer than avertin The intravenous barbiturates should be used with clinical acumen, and experience has proved that the volatile anæsthetics in common clinical use, excepting only chloroform and di-vinyl ether, may be administered to subjects with gross liver disease without producing significant exacerbation of the pre-existing liver condition.

It can be concluded that, in normal adequately oxygenated subjects, glycogen and protein depletion is mainly responsible for the intensity of the liver disfunction that may occur in the post-anæsthetic period. Anoxia pre-disposes to liver inefficiency in the post-anæsthetic period and, when it is combined with glycogen and protein depletion, and/or pre-existing liver disease, an intense degree of liver disfunction may occur in the post-anæsthetic period which may be irreversible when chloroform or di-vinyl ether have been used.

The Gastro-intestinal Tract. The commonest upset of the digestive tract produced by anæsthesia is the nausea, retching and vomiting which may occur before anæsthesia, during anæsthetic induction, during recovery and in the post-anæsthetic period.

The smell and taste of certain blood-borne anæsthetics and/or their association in the minds of a certain type of nervous subject with surgery may cause nausea, retching or vomiting even before anæsthesia commences In such subjects adequate premedication with atropine and morphia or their substitutes is essential. Although atropine in therapeutic dosage has no perceptible effect upon psychic function, it inhibits salivary, gastric and intestinal secretions but has no action on gastric movement or peristalsis Morphia in therapeutic dosage depresses attention, weakens the appreciation of external stimuli and dulls the anticipating and dread of impending events Adequate premedication with balanced

barbiturates, and reflex gastro-intestinal effects may occur during the stages of non-cooperative stupor and anæsthetic sleep. These effects vary in intensity and duration as the strength of appropriate stimuli and the length of time in the stages of non-cooperative stupor and anæsthetic sleep. The reflex effects observed are identical with those that may occur during the same period of nitrous oxide anæsthesia. During anæsthetic induction salivation may increase by 550 per cent. with di-ethyl ether, by 500 per cent. with chloroform and by 250 per cent. with cyclopropane; gastric secretion and its motility may be increased in like manner. Moreover, this irritating saliva and the anæsthetic atmosphere may be swallowed and gastric irritability accentuated. When, however, anæsthesia to the level of complete sensory loss or deeper is achieved with these anæsthetics, gastro-intestinal reflex effects cease, the secretions of the entire tract are abolished and its musculature fails to react to central or local stimulation.

A suitable combination of the anæsthetics in common clinical use permits sufficiently swift induction to the level of complete sensory loss for gastro-intestinal reflex effects to be eliminated even when these relatively irritating anæsthetics are employed. Thus, adequate premedication followed by an intravenous barbiturate injected at a proper rate permits anæsthesia to the level of complete sensory loss to be achieved with nitrous oxide and the ethers, or with cyclopropane, before recovery from barbiturate anæsthesia has fallen below this level. Gastro-intestinal reflex effects during anæsthetic induction can in this way be completely eliminated. The conclusion is that when pre-anæsthetic preparation is thorough, pre-anæsthetic medication adequate, and induction with any suitable combination of the common clinical anæsthetics swiftly carried to the level of complete sensory loss, then gastro-intestinal reflex effects are either trivial or entirely absent. But, inadequate pre-anæsthetic preparation or any factor making a long, slow induction—such as inadequate or ill-timed premedication, or incorrect methods of induction — predispose to gastro-intestinal reflex effects during anæsthetic induction.

During anæsthesia maintained at the level of complete sensory loss or deeper, the secretions of the gastro-intestinal tract are abolished and its musculature is flaccid and toneless. In this toneless condition of the œsophagus and stomach, surgical

those initiated locally in the bowel itself. In a properly prepared subject, the gastric effects possible during a long, slow induction are a source of annoyance rather than an element of danger; but when for any reason the stomach is overloaded, retching and/or vomiting during the stages of non-cooperative stupor or anæsthetic sleep is a major catastrophy that may cost the subject his life The possibility of these reflex effects is significantly reduced if induction to the level of complete sensory loss is swiftly achieved, for then the time spent in the stages of non-cooperative stupor and anæsthetic sleep—when reflex effects occur—is materially shortened and a greater measure of protection is thus afforded to the subject.

The speed with which induction to the level of complete sensory loss can be achieved in clinical anæsthetic practice depends upon the nature of the blood-borne anæsthetic employed. When evipan or pentothal is injected intravenously at a proper rate, induction to the level of complete sensory loss is so swift that the fleeting taste and smell of sulphur never produces reflex gastric effects even in the most susceptible subject. Nitrous oxide has a sweet taste and smell, resembling burnt sugar, which are not objectionable, but it is a weak anæsthetic and can produce anæsthesia only to the level of anæsthetic sleep. When used correctly, induction to the level of anæsthetic sleep is swift; but at this level of anæsthetic depression, especially when premedication is inadequate, para-sympathetic reflex effects can be produced by appropriate stimulation· there may be coughing, gagging or vomiting, salivary and gastric secretions may be augmented, and gastric movement and peristalsis throughout the whole tract invariably persists. Because the anæsthetic is weak, the anoxia which not infrequently occurs during nitrous oxide anæsthesia may produce vomiting, and invariably produces abnormally large and irregular contractions of the stomach, the ileum and the colon. There is little doubt that this excessive and irregular bowel movement is due to anoxia, for it is immediately abolished by two or three breaths of pure oxygen

The remaining inhalation anæsthetics in common clinical use, di-ethyl and di-vinyl ether, chloroform, cyclopropane and ethyl chloride, are potent anæsthetics; but in so far as their taste and smell are objectionable, they are irritants Those most soluble in water, the ethers, are the most irritating. Because they are relatively irritating, induction is slow relative to the intravenous

local irritation of the stomach and the intensity of the ketosis produced during anæsthesia.

There is evidence that the gastric mucosa is irritated by the direct action of the common inhalation anæsthetics when their concentration in the stomach is high enough. When the anæsthetic atmosphere or excess of saliva saturated with the anæsthetic is swallowed during induction, and/or when too great a positive pressure is used in subjects with an abnormally lax or dilated œsophagus, inhalation anæsthetics may enter the stomach. If the presence of the inhalation anæsthetic in the stomach is ignored, these subjects usually vomit in the post anæsthetic period: vomiting in the post-anæsthetic period is rare when inhalation anæsthetics are prevented from entering the stomach or if the stomach is emptied at the end of the anæsthetic. If an endotracheal tube is passed after a pentothal induction and the cuff inflated, or a pharyngeal pack inserted before the maintenance anæsthetic is commenced, anæsthetic gases and vapours cannot enter the stomach. When this routine is followed, vomiting and nausea are both rare even after nitrous oxide, oxygen and di-ethyl ether anæsthesia of an hour or more, and the subject is often ignorant that he has had di-ethyl ether. Vomiting is rare after anæsthesia lasting for as long as five hours with nitrous oxide, oxygen and di-ethyl ether at the level of complete sensory loss with d-tubo curarine chloride, provided that a Ryle's tube or a wide-bore stomach tube is maintained *in situ* during anæsthesia and in the post-anæsthetic period. The incidence of post-anæsthetic vomiting is also reduced by the passage of a stomach tube and/or the washing out of the stomach with a solution of sodium bicarbonate at the end of the anæsthetic. Again, Schlesinger (1912) observed that the continuous intravenous administration of a 5 per cent. concentration of di-ethyl ether in normal saline produced little vomiting in the post-anæsthetic period, but that post-operative vomiting could readily be caused by the air-swallowing that occurred when a towel was placed over the mouth to produce rebreathing during a troublesome intravenous induction. Finally, in the absence of other factors such as an overfull stomach prior to anæsthesia, the intravenous barbiturates seldom produce vomiting in the post-anæsthetic period.

manipulations may readily cause regurgitation of fluid stomach contents into the pharynx, with the attendant danger that this may be inhaled into the pulmonary system. This danger can be eliminated by the aspiration of the fluid through a stomach tube, by the passage of a cuffed endotracheal tube, or—if the anæsthetist dislikes or distrusts a cuffed endotracheal tube — by an endotracheal tube with suitable pharyngeal packing. This is the only danger to be anticipated during surgical procedures if anæsthesia to the level of complete sensory loss or deeper is maintained throughout surgical interference. If the level of anæsthetic maintenance is permitted to become lighter than complete sensory loss, the muscle tone of the gastro-intestinal musculature promptly returns Thus, Bhatia and Burn (1933) observed that in decerebrate cats the smooth muscle of the intestine promptly regained its tone when di-ethyl ether anæsthesia ceased. During abdominal surgical procedures, surgeons and anæsthetists are only too conscious of the fact that peristalsis and vomiting may occur when anæsthetic maintenance inadvertently falls below the level of complete sensory loss.

When anæsthesia ceases, and in the absence of other factors, muscle tone in the gastro-intestinal tract is rapidly regained and small contractions are observed throughout the whole tract at about the same time as movement is observed in skeletal muscles. With the return of muscle tone, vomiting may occur and as a rule begins when the non-cooperative stupor stage of anæsthetic recovery has been reached. When vomiting is not repeated, the subject is often ignorant of the fact that he has vomited, for he is amnesic at this stage of anæsthetic recovery; this is particularly so when post-anæsthetic morphia has been correctly timed.

Vomiting in the post-anæsthetic period has always been recognised as a natural sequela of anæsthesia. Waters (1938) in a survey of 10,638 anæsthetics found that vomiting occurred in the post-anæsthetic period in 23 per cent. of cases after nitrous oxide, *in 33 per cent.* after ethylene, in 39 per cent after cyclopropane, and in 56 5 per cent of cases after di-ethyl ether. This is the order of their irritability, and it is significant that it is also the order of the anæsthetic potency of these several inhalation anæsthetics. This in turn suggests the two principle factors responsible *for vomiting in the post-anæsthetic period—namely,*

those in charge of these cases that a sense of well-being during the post-anæsthetic period was significantly greater than that of the controls. And if the stomach is empty before anæsthesia, the fluid balance of the body is within normal limits, protein depletion is absent, and the glycogen content of the liver is high, then ketosis during anæsthesia and, in turn, vomiting and/or nausea during the post-anæsthetic period will be reduced to minimal proportions, provided that anoxia is avoided throughout.

Anoxia during anæsthesia or in the post-anæsthetic period is a potent cause of vomiting. Nothing will cause such intense and rapid acidosis as anoxia, and it therefore reacts synergically with the residual ketosis, produced by the level of anæsthetic depression, and so sets up post-anæsthetic vomiting. Adequate oxygenation throughout, on the contrary, combines with anæsthesia to the level of complete sensory loss to provide absolute safety with, at the same time, a minimal degree of ketosis. Since the introduction of d-tubo-curarine chloride, an efficient anæsthetic preparation for major surgery can be safely produced at the level of complete sensory loss with this muscle relaxant, and, despite surgical procedures of ever-increasing gravity and duration, the incidence of post-anæsthetic vomiting has not increased and in the opinion of some anæsthetists is thought to have diminished. This effect can be attributed in the main to adequate oxygenation and the relatively minor degree of ketosis produced by anæsthesia to the level of complete sensory loss. The intensity of ketosis can be further diminished by using anæsthesia lighter than complete sensory loss with d-tubo-curarine chloride. While this procedure results in an efficient anæsthetic preparation with even less vomiting in the post-anæsthetic period, it is achieved at the expense of safety, for reflex effects possibly endangering the life of the subject can occur at levels of anæsthesia lighter than the level of complete sensory loss.

When anæsthesia ceases, the anæsthetist must ensure that the subject is positioned in bed so that his airway is clear and so that blood and/or secretions cannot enter the pulmonary or gastro-intestinal tract. An average adult should be given morphia, 1/6 grain, as soon as he enters the non-cooperative stupor stage of recovery; but it must be remembered that post-anæsthetic morphia is contra-indicated after cerebral operations and after surgical

These data indicate that the mass of volatile blood-borne anæsthetic entering the stomach by diffusion from the stomach capillaries is too small to produce local irritation in this viscus. When however, inhalation anæsthetics are permitted to enter the stomach in significant amounts during anæsthesia, irritation of the gastric mucous membrane and vomiting in the post-anæsthetic period are readily produced. It is probable that the intense vomiting that sometimes follows cyclopropane anæsthesia must be attributed to this cause. It must be remembered, too, that the presence of blood in the stomach is a powerful gastric irritant.

If local irritation of the stomach is successfully prevented, then vomiting in the immediate post-anæsthetic period can be attributed to the intensity of the ketosis produced during anæsthesia and, in the remote post-operative period, to the complications which may follow surgical interference.

Evidence has been discussed which indicates that the degree of metabolic upset during anæsthesia varies as the intensity of the ketosis produced, and this in turn is determined by the depth and duration of anæsthesia. Hence, vomiting is commoner with potent anæsthetics such as di-ethyl ether and chloroform; but in the absence of other factors, it varies as the level of anæsthetic depression rather than as the anæsthetic used to produce this level of anæsthetic depression. Its incidence will also vary as the pre-anæsthetic condition of the particular subject. Thus the stomach may be overloaded prior to anæsthesia, vomiting and/or deficient fluid intake may have upset the water balance of the body, and curtailment of the subject's food intake may have produced carbohydrate and/or protein depletion These effects are not infrequent in obstetric cases, which may also present varying degrees of liver inefficiency due to the toxæmias of pregnancy. Carbohydrate depletion is corrected by the administration of sweets or glucose in the twenty-four hours prior to anæsthesia. Protein depletion is avoided by an adequate protein diet in the pre-anæsthetic period and can be corrected by the administration of methionine in the twenty-four hours prior to anæsthesia. Three grams of methionine on the day prior to anæsthesia followed by two grams five hours before anæsthesia were administered to a series of more than 200 subjects The incidence of vomiting did not fall below 10 per cent but was equal in both sexes, and it was the impression of

the anæsthetist can do to prevent it. Women commonly vomit about twice as frequently as men. The best prophylactic in such a subject is adequate pre-anæsthetic medication and correctly-timed post-anæsthetic morphia combined with efficient nursing. It is well to remember that morphia produces emesis in certain subjects: omnopon or pethidine should then be substituted for morphia. When such psychic factors can be eliminated, it is conventional to regard post-operative vomiting which persists for longer than twenty-four hours as a surgical complication. But it is observed that the return of the tone of the smooth muscle of the gastro-intestinal tract in the non-cooperative stupor stage of anæsthetic recovery is occasionally delayed; again, abdominal distention of varying degree is an almost constant sequela of a laparotomy. These two effects are probably complementary to one another and in each instance they can be partly attributed to the state of anæsthesia. If it is supposed that the gaseous content of the bowel is high before anæsthesia, then, when the muscles of the gastro-intestinal tract and the abdominal wall are relaxed during anæsthesia, distention may occur and particular segments of toneless bowel may become overdistended. Again, during a laparotomy the bowel delivered from the peritoneal cavity may be distended with gas and it is observed that the longer it remains exposed, the greater is the distention. At the completion of surgical interference this distended bowel may regain its tone, but it may react after the fashion of an overdistended bladder and fail to contract as long as it is overdistended. It is significant that the rapid excretion of the nitrogen content of this overdistended bowel produced by oxygen therapy (as described by Fine *et al.* [1936]) reduces distention and often permits the paralysed bowel to regain its tone. The same result is often achieved when a Miller-Abbott tube is passed into the stomach, jejunum or ileum.

The Uterus. The behaviour of the non-pregnant uterus during anæsthesia is of no clinical interest or practical importance In contrast, when pregnancy occurs a series of physiological readjustments is set in train which makes the mother and her developing child a special subject for anæsthesia. It is essential to ascertain if the response of a pregnant woman to anæsthesia differs from that of her non-pregnant sisters and how the fœtus *in utero* reacts to anæsthetics administered to its mother. Finally, when term is

procedures on the naso-bucco-pharynx when the danger of bleeding into the pulmonary or gastro-intestinal tract requires the early return of consciousness and the rapid return of an effective cough. Oxygen should be administered when required, and, if vomiting occurs, asphyxia and the aspiration of vomitus must be prevented. When the co-operative stupor stage of recovery has been reached, and for the next 12 - 24 hours, only fluids should be given by mouth and the subject should be encouraged to take frequent sips: for a large drink may cause vomiting.

Hence, the several occasional factors responsible for post-anæsthetic vomiting can be eliminated or reduced to minimal proportions by thorough pre-anæsthetic preparation; by adequate pre-anæsthetic medication; by a swift and trouble-free induction to the level of complete sensory loss; by preventing irritating gases and vapours from entering the stomach (or by evacuating them if this has occurred); by anæsthesia maintained at the level of complete sensory loss throughout; by efficient post-anæsthetic medication and nursing; and by adequate oxygenation throughout the whole period of anæsthetic induction, maintenance and recovery. When these occasional factors are so controlled, the intensity of post-anæsthetic vomiting is mainly due to the intensity of the *ketosis produced by anæsthesia to the level of complete sensory loss.* Anæsthesia to this level of depression does not produce intense ketosis, and the incidence of vomiting in modern anæsthetic practice is seldom so high as that reported by Waters. Thus, at a hospital where anæsthetic specialists administer mostly pentothal followed by cyclopropane or nitrous oxide and di-ethyl ether, with or without d-tubo-curarine chloride, the incidence of post-anæsthetic vomiting in subjects aged 60 - 70 years proved to be 10 per cent. of cases In a series of cases at a teaching hospital where anæsthetic clerks administer, as a rule, pentothal followed by nitrous oxide and di-ethyl ether with or without d-tubo-curarine chloride, the incidence of post-anæsthetic vomiting was again 10 per cent of cases; and it was observed that in unprepared subjects —the take-in cases—the incidence of vomiting was significantly greater than in those subjects whose pre-anæsthetic preparation had been thorough and complete

A certain type of nervous subject will vomit in the post-operative period and may continue to do so in spite of everything

abortion while after the twelfth week of pregnancy this is a remote possibility. When surgery must be performed during pregnancy, it is a wise prophylactic measure to give a daily dose of 10 milligrams of progesterone hypodermically, for two days before and for seven days after operation, for this may inhibit uterine irritability. Surgical interference for obstetric emergencies such as ectopic gestation, abruptio placenta, placenta prævia, etc., and for surgical emergencies such as appendicitis, cholecystitis, intestinal obstruction, etc., must be undertaken regardless of the stage of pregnancy.

There are, however, certain systemic disorders associated with pregnancy which may raise grave problems for the anæsthetist. Anæmia may occur during pregnancy. Microcytic anæmia, which is relatively common, is due to deficiency of iron in the diet; and in macrocytic anæmia a major factor may be a deficiency in the uptake of animal protein. In view of the excessive blood loss which may occur during parturition, anæmia of this origin should be corrected by efficient ante-natal treatment. Subjects with impaired cardiac reserve require special antenatal treatment and introduce anæsthetic hazards during pregnancy and labour and in the puerperium. They may be grouped into those without dyspnœa, those with slight dyspnœa on exertion, and those with dyspnœa on slight exertion Rheumatic cardiac sequelæ such as mitral stenosis give rise to greatest anxiety; when cardiac failure has occurred during one pregnancy it is observed that similar symptoms occur at an earlier date during the next pregnancy. In such subjects trivial events may precipitate cardiac failure. Thus, intelligent graduated exercises, adequate diet and rest, antenatally, may prevent cardiac failure during pregnancy in a subject with mitral stenosis, in such a subject, if labour is normal and short, cardiovascular distress may be of a minor nature or may even be avoided altogether On the other hand, an ill-nourished anæmic subject with a mild cardiac lesion in poor circumstances where adequate antenatal rest is impossible may develop severe or even fatal cardiac failure when subjected to the additional stress of a twin pregnancy with a mild toxæmia or a difficult labour with perhaps excessive blood loss. During the last month of pregnancy the size of the uterus may further embarrass the cardiac subject. Pressure effects which impede breathing may intensify an

reached, it is important to consider how normal labour is modified by anæsthetics.

During pregnancy the basal metabolic rate is increased by about 25 per cent., and *the minute-volume of blood flow is increased in* the later months of pregnancy by 45 - 85 per cent. Thomson *et al* (1938) showed that the total blood volume is increased by 45 per cent., plasma volume by 65 per cent., and the total cell volume by 16 per cent. The examination of such blood indicates a fall of hæmoglobin to about 80 per cent. of normal but the absolute increase of erythrocytes, together with the increased circulatory rate, results in increased oxygen transportation. A hæmoglobin value of 80 per cent. (Haldane) is now regarded as normal during pregnancy. During the last three months of pregnancy blood calcium is slightly lowered, the alkaline reserve is diminished, and bile pigments and cholesterol are slightly increased Blood fibrinogen increases by about one-third and rises still further during labour; blood platelets increase almost threefold; and Wright (1942) has shown that there is a diminution in the rate of venous blood flow in the lower extremities. The renal pelves and the ureters dilate, and there is said to be a slight diminution in liver function but the blood urea is low. There is need for a liberal carbohydrate diet during pregnancy and ketosis may readily be precipitated with acetone in the urine. Pregnancy is a harmonious symbiosis. Baird (1950) states· " It cannot be said too often and too clearly that pregnancy is a normal state and that in a healthy woman the complex physiological readjustments required involve little disturbance and no danger."

A normal pregnant woman reacts to anæsthesia in a manner similar to her non-pregnant sister surgical interference during pregnancy carries no risk of interrupting gestation unless it involves the internal genital organs or the cervix, when there is a slight but definite risk of abortion or miscarriage. The earlier in pregnancy such surgical interference occurs, the greater is the chance of interrupting gestation. Whenever possible, surgical interference *should be postponed until after delivery.* Operations which are necessary but which are not surgical emergencies—such as the removal of an ovarian cyst, degenerating fibroids, etc —should be postponed until after the twelfth week of pregnancy, for if the corpus luteum is removed before this time there is a great risk of

reason to believe that spinal anæsthesia introduces avoidable maternal risks during the last three months of pregnancy. In all subjects with impaired cardiac reserve spinal anæsthesia introduces the risk of cardiovascular distress, and in pregnant women with cardiac involvement this risk is very significantly increased. In the Obstetric Department of Guy's Hospital spinal anæsthesia is never used for the obstetric complications of pregnancy but only on the exceedingly rare occasions when it is indicated by a non-obstetric complication of pregnancy. On the other hand, local anæsthetics used by methods other than spinal anæsthesia do not significantly depress the cardiovascular system and no exacerbation of a maternal pre-existing cardiac involvement is observed when local infiltration or the technique of peridural nerve block, known as sacral anæsthesia, is used during pregnancy. Hence the cardiovascular system of a pregnant woman with pre-existing cardiac involvement is not significantly depressed if anæsthesia is produced with a combination of blood-borne anæsthetics (excepting only chloroform, cyclopropane and trichlorethylene) and if muscular relaxation is produced with these blood-borne anæsthetics, with d-tubo-curarine chloride, or with a form of local anæsthesia other than spinal anæsthesia The only qualification to this generalization is that the level of anæsthetic depression must be sufficiently deep to abolish cardiovascular reflex effects and that oxygenation and venous return must be adequate throughout. If these conditions are fulfilled neither anoxæmia nor stagnant anoxia can occur in the mother and no exacerbation of the maternal cardiac condition is likely. Moreover, by the effective support of the maternal cardiovascular system, the principle danger to the fœtus—anoxia—will be avoided.

Vomiting is a common accompaniment of pregnancy. Morning sickness may occur early in pregnancy and is usually transitory and of little significance. It may, however, progress to hyperemesis gravidarum, with ketosis of varying degrees, dehydration, chloride loss, jaundice and fatty infiltration of the liver, and an acute exacerbation of a pre-existing diabetes mellitus may occur. Vomiting may occur during the toxæmias of pregnancy such as the pre-eclampic states, eclampsia, hypertensive states and acute yellow atrophy of the liver. It may also be associated with the pyelonephritis which occurs in 5 per cent. of all pregnancies, with

associated bronchitis, and oxygen therapy may be necessary in an emphysematous subject or during an asthmatic attack. In a normal subject, pressure of this origin may produce peripheral vascular effects such as hæmorrhoids, varicosities and œdema of the lower extremities; and when the diminished rate of venous leg flow is coupled with the increased fibrinogen and platelet content of blood, peripheral thrombosis and pulmonary embolism clearly become a real danger. In the cardiac subject these dangers are intensified, the more so when stagnant anoxia occurs. Cerebral emboli rarely occur during labour or in the puerperium, but cerebral hæmorrhage is always possible in the hypertensive states associated with the toxæmias of pregnancy and is the commonest cause of death in eclampsia. The ability of the cardiovascular system of these subjects to withstand the stresses of pregnancy and labour depends largely upon the effectiveness of antenatal treatment and the character and duration of labour. If antenatal treatment has been efficient, and if labour is short without excessive blood loss or anoxia, only those subjects with dyspnœa on slight exertion present major difficulties to the anæsthetist.

When maternal cardiovascular distress is present or is to be anticipated because of pre-existing cardiac involvement or the presence or possibility of excessive blood loss, blood-borne anæsthetics which may directly depress the heart—*e.g.*, chloroform. cyclopropane and trichlorethylene, should not be used. The remaining blood-borne anæsthetics in common clinical use do not depress the cardiovascular system if anoxia and anæsthetic overdose are avoided throughout The use of spinal anæsthesia in pregnant women is a controversial subject. Even if the possibility of post-spinal nervous sequelæ is ignored, the discussion in Chapter XVIII indicates the inevitable danger of cardiovascular distress which follows the use of spinal anæsthesia in subjects with impaired cardiac reserve. These conclusions apply even more forcibly in pregnant women with pre-existing cardiac involvement, for the paralysis of a field of peripheral resistance in these subjects makes a yet greater demand upon the already embarrassed heart; and, moreover, during the last three months of pregnancy venous return is sluggish. During this period, too, these subjects are normally prone to peripheral vascular effects and a fall of blood-pressure must intensify the danger of thrombosis and embolism. There is

anæsthesia should be reduced to minimal proportions by the shortest and lightest anæsthetic that is compatible with the pregnant woman's safety and with an efficient anæsthetic preparation for the proposed surgical procedure. Anæsthesia to the level of complete sensory loss has been seen to be the lightest level of anæsthetic depression compatible with complete safety, and muscular relaxation adequate for any surgical procedure can be produced with local infiltration or with d-tubo-curarine chloride. When anæsthesia to the level of complete sensory loss with adequate oxygenation throughout is combined with such muscle relaxants, the residual ketosis produced is slight and may be further reduced or controlled by the use of insulin and glucose as pre-anæsthetic medicants and by intravenous glucose therapy during anæsthesia and in the post-anæsthetic period. Anoxia must be avoided at all costs, for anoxia rapidly intensifies the harmful factors acting in ketosis.

The use of local infiltration or d-tubo-curarine chloride materially reduces the depth of anæsthesia required to produce an efficient anæsthetic preparation and, in turn the intensity of residual ketosis As narcotics, local anæsthetics produce ketosis in keeping with the mass of local anæsthetic injected, and the degree of loss of muscle tone produced by them varies as the care and skill with which they are administered. The intravenous injection of d-tubo-curarine chloride in an effective dose rapidly produces complete loss of muscle tone, and—since it is not a narcotic—does not produce ketosis. On this account, it is the more valuable muscle relaxant when pre-existing ketosis is present but the safety of this relatively new anæsthetic adjuvant during pregnancy may be questioned by some anæsthetists. It has been said that d-tubo-curarine chloride fails to pass through the placental membrane It has a molecular weight of 657, and it would be more correct perhaps to assume that its slow rate of diffusion through the placental membrane (coupled with the relatively rapid rate of its excretion by the mother) prevents its accumulation in an effective concentration in the fœtus *in utero*. It is known that the ACh content of the placenta is high and this may be an additional deterrent. But even if an effective concentration of d-tubo-curarine chloride could be achieved in the fœtus, the loss of muscle tone in all fœtal striated muscles including the

chronic nephritis and with cortical necrosis of the kidneys. The significance of these associated disorders of pregnancy to the anæsthetist is the degree of maternal ketosis and/or liver or renal inefficiency which they produce.

If liver inefficiency is present or is suspected because of an associated toxæmia of pregnancy, chloroform and di-vinyl ether are contra-indicated and anoxia should be avoided at all costs because of the danger of an acute diffuse necrosis of the liver in the post-anæsthetic period. Reactive non-volatile anæsthetics, such as evipan and pentothal, should be avoided or used with the utmost clinical acumen, for the detoxication of such anæsthetics is sluggish and/or faulty when liver inefficiency is present; in consequence, overdose may readily occur. It should be remembered too, that detoxication by the liver is an essential pre-requisite to the clearance of local anæsthetics from the blood stream. On the other hand, in tropical zones where liver inefficiency is common, clinical experience has shown that subjects with the most extreme degree of liver inefficiency can be safely anæsthetised with a volatile anæsthetic—excepting only chloroform and di-vinyl ether —if adequate oxygenation is maintained throughout and such an anæsthetic produces no exacerbation of the pre-existing liver condition. The administration of glucose gives added protection; it is the writer's opinion that methionine therapy is indicated, though its value is not yet proven

When adequate oxygenation is maintained throughout, it has been concluded that the anæsthetics in common clinical use—excepting *only chloroform—do not* exacerbate a pre-existing renal condition. The obligatory route of the excretion of non-reactive, non-volatile anæsthetics, however, is the kidneys, and when repeated doses of these hypnotics are administered during pregnancy in the presence of renal inefficiency, accumulation can occur, with overdose.

Finally, ketosis alone or combined with hepatic and/or renal inefficiency may occur during pregnancy; and a pregnant diabetic woman *may readily become* un-balanced Anæsthesia produces a residual ketosis which varies in intensity as the depth and duration of anæsthesia At all times, but particularly when ketosis is present in the pre-anæsthetic period, this residual ketosis incident to

introduces the risk of interrupting the pregnancy provided that maternal anoxia is avoided throughout.

Unless one of the systemic disorders that are associated with pregnancy is present, it can be concluded that the administration of an anæsthetic during pregnancy neither introduces special hazards to the mother or the fœtus nor endangers the normal course of gestation if maternal cardiovascular distress and anoxia are avoided throughout. An ill-considered anæsthetic administered to a pregnant woman suffering from cardiovascular, hepatic, or renal inefficiency and/or ketosis, may terminate the pregnancy and/or result in the mother's death during anæsthesia or in the post-anæsthetic period. On the other hand, if the hazards associated with the systemic disorders of pregnancy are recognised, a correctly determined anæsthetic does not endanger the life of mother or fœtus, and the normal course of gestation is not threatened if anoxia is avoided throughout. If maternal anæsthesia is sufficiently prolonged, the fœtal brain at length reaches anæsthetic equilibrium with the maternal brain and the anæsthetic atmosphere to which the mother is exposed, but no harm accrues even when surgical anæsthesia is produced and the fœtus recovers from this level of anæsthetic depression at approximately the same rate as the mother. In clinical dosage d-tubo-curarine chloride can be safely used during pregnancy.

The fœtus developing *in utero* obtains its oxygen and all other substances necessary for its continued growth and existence from maternal blood, and it excretes into maternal blood the waste products of its metabolism. This exchange is effected by the placenta. The minute-blood flow through the uterus and in turn through the maternal side of the placenta increases enormously during pregnancy. Early in pregnancy the oxygen needs of the tiny fœtus are small but as pregnancy advances the oxygen demands of the growing fœtus gradually outpace the increased blood flow to the uterus. At about sixteen days after conception, maternal and embryonic bloods are separated by four layers which have a total thickness of 0 2 mm From the twentieth week of pregnancy onwards only two layers, the vascular endothelium and the syncitium, separates the two bloods and the syncitial layer progressively thins as pregnancy advances. Wright (1942) states that the endothelium of the fœtal capillaries in the placenta is

diaphragm could have no effect upon the oxygenation of the fœtus *in utero*, and in clinical dosage no other effect can be anticipated. There is evidence, too, that d-tubo-curarine chloride has no effect upon the uterus during pregnancy and that its use in clinical practice neither effects the normal development of the fœtus nor threatens the normal course of gestation. Thus, a pregnant woman with an acute depression received electrical shock therapy on sixteen separate occasions during the sixth and seventh months of her pregnancy. At each treatment 0 5 grams of pentothal followed by atropine gr. 1/50th, and 30 milligrams of d-tubo-curarine chloride was given intravenously prior to the electric shock. This produced complete loss of muscle tone in all maternal striated muscles including the diaphragm; but the uterus, which was readily palpable through the relaxed abdominal wall, retained its normal tone. The passage of the electric current produced the characteristically feeble, controlled, clonic contraction of maternal striated muscle, without alteration of uterine tone; but, after a delay of from 45 to 60 seconds, there was a firm contraction of the uterus lasting for about one minute. This woman recovered from her depression and was delivered normally of a healthy babe of 7 lbs at term. It is significant that 30 milligrams of d-tubo-curarine chloride failed to abolish normal uterine tone. The firm tonic contraction of the uterus which occurred about one minute after the electric shock may have been a normal uterine contraction, but its time-relation to the electric shock on sixteen occasions makes this unlikely. It can be attributed to the copious flood of motor impulses to all parts of the body, including the uterus, produced by the electric shock, and the delayed effect can be explained by the time taken to accumulate an effective concentration of the chemical transmitter at uterine neuromuscular junctions ACh is known to be one of the chemical transmitters of the uterus and the result observed suggests either that d-tubo-curarine chloride failed to achieve a concentration in the uterus sufficient to inhibit the action of released ACh or that some other chemical transmitter was responsible for this tonic contraction of the uterus These effects—observed in the same woman on sixteen separate occasions over a period of ten weeks—indicate that d-tubo-curarine chloride in large clinical dosage, viz. thirty milligrams, fails to inhibit uterine tone and neither harms the fœtus nor

by only 3·5 mm. of mercury. These results indicate that oxygen diffuses with difficulty, and carbon dioxide with relative ease, through the placental membrane during the last weeks of pregnancy and that the placental membrane is less permeable to the passage of the respiratory gases than is the respiratory membrane. They also emphasise the extreme danger of maternal anoxæmia to the fœtus during the last weeks of pregnancy. During a normal pregnancy there is little doubt that maternal anoxia is the gravest and perhaps the only danger to the fœtus; but, when anæsthetics are administered during a normal pregnancy, there is little reason to anticipate harm to the mother or the fœtus if the mother is adequately oxygenated throughout and maternal cardio-vascular distress is avoided.

When a blood-borne anæsthetic is administered to a pregnant woman, the mother reacts to the anæsthetic more rapidly than does the fœtus; it is a striking experience to observe a mother anæsthetised to the level of complete sensory loss or deeper, delivered by cæsarian section of an infant who commences to cry within thirty to sixty seconds after it has entered its new environment. This effect cannot be attributed to a specific resistance of the brain of the fœtus at term to anæsthetics, for if the pregnant woman is subjected to a sufficiently prolonged anæsthetic before the child is delivered, either by cæsarian section or at the end of the second stage of a normal labour, the child will be anæsthetised. The apparent resistance of the fœtus *in utero* to blood-borne anæsthetics administered to its mother can be attributed to the slower rate of absorption of the anæsthetic by the fœtal brain than by the maternal brain.

Regarding the uptake of blood-borne anæsthetics, the fœtus *in utero* can be looked upon as another maternal organ; and the rate at which it achieves anæsthetic equilibrium with an anæsthetic atmosphere of constant composition administered to its mother is determined by the absorption coefficient of the fœtus for the given anæsthetic This in turn depends upon the absorptive capacity of the fœtus for the particular anæsthetic and (assuming that the placental membrane is freely permeable to this anæsthetic) upon the volume of blood flow per unit-time through the maternal side of the placenta. If the whole body of the fœtus has the same coefficient of solubility for nitrous oxide as the body of an adult,

much thicker and presumably much less permeable than the endothelium of the pulmonary capillaries. It has been seen that carbon dioxide diffuses with ease, and oxygen with difficulty, through the respiratory membrane in the time available for gaseous exchange, and it is important to examine the diffusion rate of these respiratory gases through the thicker and less permeable placental membrane.

Most of our knowledge of placental function is obtained from the animal experiments of Barcroft (1946), Roos and Romijn (1938) and others. There is reason to believe that up to about the thirty-second week of pregnancy, respiratory exchange across the placental membrane is favourable to the adequate oxygenation of the fœtus. During this period of pregnancy the fœtal vascular bed in the placenta relative to blood actually circulating in the fœtus is large, and the permeability of the placental membrane is diminishing as pregnancy advances. Fœtal blood-pressure and the hæmoglobin content of fœtal blood progressively increases and fœtal hæmoglobin (which in animals and Man differs from maternal hæmoglobin) combines with and releases oxygen at a relatively low oxygen pressure. These several factors combine to favour the ready exchange of respiratory gases between maternal and fœtal blood. From the thirty-second week of pregnancy onwards to term, however, fœtal respiratory conditions deteriorate. The proportion of fœtal blood in the placenta relative to that in the fœtus, is reduced, other favourable factors also are approaching the limit of their usefulness and there is reason to believe that the physiological reserve of the placental mechanism at term has reached a low level. Thus, Flexner *et al.* (1948) observed that the passage of labelled sodium chloride through the placenta increased seventy-fold from the ninth to the thirty-sixth week and then decreased rapidly from the thirty-sixth week to full term This might indicate a diminished permeability of the placental membrane during the last weeks of pregnancy. Again, the difference in the oxygen pressure in the blood of the uterine artery and the umbilical vein in the last weeks of pregnancy was found to be 55 mm of mercury in sheep (Barton, 1946) and 58·5 mm of mercury in cows (Roos and Romijn, 1938). On the other hand, Roos and Romijn found that the carbon dioxide tension in the blood of the umbilical artery and venous maternal blood differed

same trend. Although these figures are only very approximate, they indicate without doubt that an effective concentration of the blood-borne anæsthetics in common clinical use is achieved in the fœtal brain at a slower rate than in maternal brain but it is clear that if anæsthesia is sufficiently prolonged anæsthetic equilibrium is at length achieved between maternal brain, fœtal brain and the anæsthetic atmosphere to which the mother is exposed.

There is reason to believe that the estimated absorption coefficients for fœtal brain shown in Table 62 are too high. It is known that the proportion of fœtal blood in the placenta is smallest at term. This is compensated for in a measure by the greater absorptive capacity of fœtal blood, relative to that of maternal blood for some blood-borne anæsthetics. Helliwell and Hutton (1950) observed that in sheep the absorptive capacity of fœtal blood for trichlorethylene was greater than that of maternal blood, and the discussion on page 136 indicates the probability that this is also true of all anæsthetics with an oil/water partition coefficient of 3·4 and more. It is thought, too, that the estimated minute-blood flow to the fœtal brain used in this calculation is too high. Finally, it is known that the placental membrane at term is less permeable than the respiratory membrane, which, as Table 16 shows, impedes the passage of some at least of the respiratory and anæsthetic gases and vapours. Hence, the uptake of blood-borne anæsthetics by the fœtal brain cannot be quicker, and is in all probability slower, than is represented by the values shown in Table 62.

Any water-soluble organic substance or electrolyte of low molecular weight readily diffuses across the placental membrane All the anæsthetics in common clinical use—even morphia whose molecular weight is 285, pass through the placental membrane and produce their characteristic action on the fœtus; but there is no data of the relative speed at which individual blood-borne anæsthetics diffuse through the placental membrane.

At term the several factors which influence the exchange of respiratory and anæsthetic gases and vapours through the placental membrane have reached the limit of their usefulness, and it has been seen that at term carbon dioxide almost assumes a state of gaseous equilibrium between fœtal and maternal blood while oxygen fails conspicuously to achieve this end in the time

then, from the values and method employed in constructing Table 26, the absorptive capacity of a human fœtus weighing 7½ lbs. is estimated to be 1623 c.c. of nitrous oxide. Baird (1950) states that the minute-blood flow through the maternal side of the placenta is of the order of 1000 c.c. and with each round of blood it is calculated that 206 c.c. of nitrous oxide is carried to the placenta.

TABLE 62.

ESTIMATED ABSORPTION COEFFICIENTS OF

	Maternal brain	Fœtal brain
Acetylene	10/14	10/21
Di-ethyl ether	10/16	10/22
Nitrous oxide	10/16	10/25
Ethylene	10/22	10/36
Cyclopropane	10/41	10/60
Chloroform	10/39	10/60

NOTE *It is assumed that the placental membrane is freely permeable and that the absorptive capacities of fœtal and maternal blood are identical*

If the diffusion of nitrous oxide across the placental membrane is free and unimpeded, and if the fœtal blood flow through the placenta is sufficient to accept this mass of nitrous oxide in the time available, then the absorption coefficient of the whole body of the fœtus for nitrous oxide is 10/80—which reference to Table 26 shows is slightly greater than that of the maternal liver. We are concerned, however, not with the rate of uptake of the anæsthetic by the fœtal body taken as a whole, but with the rate of its uptake by the brain of the fœtus. The brain of a 7½ lb. fœtus weighs about 400 grams and if it has the same coefficient of solubility for nitrous oxide as maternal brain, its absorptive capacity for nitrous oxide is calculated to be 172 c c. If it is assumed that the fœtal brain receives one-third of the nitrous oxide absorbed by the whole fœtus per round of maternal circulation, *i e.* about 70 c c of nitrous oxide, then its absorption coefficient for nitrous oxide is of the order of 10/25 while reference to Table 26 shows that the absorption coefficient of the maternal brain for nitrous oxide is 10/16. The absorption coefficients of maternal and fœtal brains for several common blood-borne anæsthetics calculated in this manner are shown in Table 62 and exhibit the

anæsthetised and, in the absence of fœtal anoxia, may not breath spontaneously for some time. After prolonged nitrous oxide or ethylene anæsthesia without anoxia, the new-born babe invariably breathes as soon as fœtal anoxia has been relieved. Finally, when cyclopropane, chloroform or trichlorethylene are used during parturition without overpressure, the adequately oxygenated new-born babe invariably breathes as soon as it enters its new environment. Organe (1950) states that fœtal respiration continues in the presence of full maternal anæsthesia with cyclopropane; but with cyclopropane, as with all the other potent anæsthetics discussed, this result must depend entirely on the duration of anæsthesia and the absence of overpressure. We have no data to gauge the diffusion velocity of d-tubo-curarine chloride across the placental membrane but it is slower than that of the inhalation anæsthetics discussed. Since its molecular weight is high, viz. 657, and because an effective maternal dose of d-tubo-curarine chloride is excreted within about twenty minutes by a conscious or lightly anæsthetised adult, it is assumed that an effective dose is not absorbed by the fœtus in the time available. Clinical experience of the use of d-tubo-curarine chloride for cæsarian section appears to confirm this assumption.

As long as the fœtus is dependent upon the placental mechanism the anæsthetic depression of the fœtus is of no clinical importance; and it has been concluded that a correctly determined anæsthetic during pregnancy harms neither the mother nor the fœtus, if maternal anoxia and cardiovascular distress are avoided. At term, however, when the fœtus is about to sever abruptly its connection with the placenta, the rate of uptake of blood-borne anæsthetics by the fœtal brain becomes a matter of paramount importance. In a full-term fœtus the neuromuscular reflexes responsible for breathing, sucking and swallowing are well established and even a premature child of 7 - 8 months possesses all the reflexes essential for its survival. On entering its new environment, a healthy, adequately oxygenated new-born babe immediately begins spontaneous breathing and is responsible for its own oxygenation. If developmental errors and birth injuries are excluded, the initiation of spontaneous respiration is likely to be delayed only by the depression of fœtal central nervous system produced by anoxia or anæsthesia. The administration of an

available for gaseous exchange between these two systems. Using these two respiratory gases as standards, it can be assumed that anæsthetics whose diffusion velocity is greater than carbon dioxide pass rapidly through the placental membrane; those with a diffusion velocity less than carbon dioxide and greater than oxygen diffuse through the membrane less rapidly; and anæsthetics whose velocity of diffusion is less than that of oxygen diffuse slowly through the membrane.

As a mechanism for gaseous exchange, the placental system is similar to the mechanism of exchange between alveolar air and blood flowing in the pulmonary capillaries for in each instance the separating membrane consists of two endothelial layers supported on a basal membrane. In the absence of experimental data it can be assumed that the relative order of the diffusion velocity of the respiratory and anæsthetic gases and vapours through the placental membrane is the same as through the respiratory membrane, but that the absolute diffusion velocity is reduced in each instance, for the placental membrane is thicker and presumably less permeable than the respiratory membrane. If this assumption is justified, then reference to Table 16 indicates that the ethers, ethyl chloride and acetylene, whose diffusion velocity is greater than that of carbon dioxide, diffuse readily through the placental membrane; and the values shown in Table 62 are a fair representation of the relative speed of the anæsthetic depression of the maternal and fœtal central nervous systems. Nitrous oxide and ethylene, whose diffusion velocity is less than that of carbon dioxide and greater than that of oxygen, diffuse less swiftly through the placental membrane; and when these anæsthetics are administered to the mother, *the fœtal brain is depressed* more slowly than is indicated by the values shown in Table 62. Finally cyclopropane, chloroform and trichlorethylene diffuse with difficulty through the placental membrane, for their diffusion velocity is slower than that of oxygen The uptake of these anæsthetics by the fœtal brain is very slow and it is depressed at a rate significantly slower than is indicated by the values shown in Table 62. These conclusions coincide with the results observed when an anæsthetic atmosphere of constant composition is administered to a mother at term. When prolonged di-ethyl ether anæsthesia is administered during parturition, the new-born babe is likely to be

ignored; and adequate atropine, which does not inhibit uterine action or depress the fœtus, should always be used as a pre-anæsthetic medicant. Emotional stress during local infiltration can be abolished or reduced to minimal proportions with adequate premedication with a suitable hypnotic; but if premedication with morphia or barbiturate preparations is heavy or ill-timed, the central nervous system of the babe will be depressed. Emotional stress during local infiltration can be eliminated without depressing the central nervous system of the fœtus if, after adequate atropine, nitrous oxide or ethylene is administered without oxygen lack, for both are weak anæsthetics whose uptake by fœtal brain is relatively slow; since they are rapidly excreted, the fœtal central nervous system is not significantly depressed if anoxia is avoided throughout.

De Lee and Greenhill (1947) state that local infiltration is the best anæsthetic for cæsarian section and Marshall (1947) and others share their opinion. Quite apart from the danger of reflex effects, many obstetricians dislike operating on a conscious subject under local infiltration. Both objections can be eliminated with adequate pre-anæsthetic atropine followed by nitrous oxide or ethylene anæsthesia without oxygen lack.

The suitability of spinal anæsthesia for cæsarian section is one of the most controversial questions in anæsthesia. In the past the most authoritative opinions regarded spinal anæsthesia as dangerous in obstetrics. De Lee and Greenhill (1947) and Bourne and Williams (1948) hold definitely to this opinion, and Baird (1950) states that many believe spinal anæsthesia to be dangerous in pregnancy On the other hand, in this country and in America, a number of anæsthetists are using spinal anæsthesia for cæsarian section with success. Thus, Weintraub and Merrian (1943) reported a series of 345 cæsarian sections performed under spinal anæsthesia without a maternal death, Resnick (1945) 137 cases with no maternal deaths, Thomas (1947) 346 cases without a maternal death and Malkin (1947) 736 cæsarian sections without a maternal death that could be attributed to the spinal anæsthetic.

During spinal anæsthesia, the local anæsthetic used can have no action on the fœtus *in utero* When a successful spinal anæsthetic is produced to the level of dorsal 11, the blocking of the spinal nerve roots as they cross the subarachnoid space produces

anæsthetic to a mother for the delivery of her child either by cæsarian section or *per via naturalis* therefore introduces an anæsthetic hazard absent from anæsthesia during pregnancy; during cæsarian section or normal labour in addition to maternal hazards, it is imperative to ensure that the central nervous system of the new-born babe is not depressed by anoxia and/or anæsthesia to a degree which prevents it from reacting to its new environment and breathing spontaneously.

When local anæsthesia is correctly used for cæsarian section, the concentration of the local anæsthetic absorbed into maternal blood is below the minimal threshold concentration necessary to depress the central nervous system of the mother and the fœtus. In the absence of maternal anoxia or cardiovascular distress the fœtus therefore runs no anæsthetic risk and breathes spontaneously immediately it is delivered. Hence, if the anæsthetist produces a safe and efficient maternal local anæsthetic preparation for the surgeon, there is no anæsthetic risk to the mother or the child. In clinical anæsthetic practice, local anæsthetics are used for cæsarian section by the techniques of local infiltration, spinal nerve block and peridural nerve block such as sacral anæsthesia.

If local infiltration is completely successful in a placid type of woman this anæsthetic preparation is ideal for cæsarian section, for the anæsthetic has not increased the maternal risk, the surgeon has a convenient and comfortable field in which to work (though this may be denied by some), the central nervous system of the fœtus is not depressed either by anoxia or the local anæsthetic, and the babe breathes spontaneously as soon as it is born. In clinical practice, however, such placid types are not common in pregnant women at term and the technique of local infiltration increases the time during which the conscious subject must submit to operative interference. Moreover, even when local infiltration is efficient, tissues must be handled gently, and too enthusiastic retraction of (for example) the bladder causes intense discomfort and mental anxiety Finally, since local infiltration does not inhibit uterine tone, this may hinder the rapid delivery of the infant. In this discussion the dangers of the reflex effects which may result from emotional and/or physical stress have been emphasised. In the writer's opinion grave and unwarranted maternal risks are incurred if these possible reflex effects are

ignored; and adequate atropine, which does not inhibit uterine action or depress the fœtus, should always be used as a pre-anæsthetic medicant. Emotional stress during local infiltration can be abolished or reduced to minimal proportions with adequate premedication with a suitable hypnotic; but if premedication with morphia or barbiturate preparations is heavy or ill-timed, the central nervous system of the babe will be depressed. Emotional stress during local infiltration can be eliminated without depressing the central nervous system of the fœtus if, after adequate atropine, nitrous oxide or ethylene is administered without oxygen lack, for both are weak anæsthetics whose uptake by fœtal brain is relatively slow; since they are rapidly excreted, the fœtal central nervous system is not significantly depressed if anoxia is avoided throughout.

De Lee and Greenhill (1947) state that local infiltration is the best anæsthetic for cæsarian section and Marshall (1947) and others share their opinion. Quite apart from the danger of reflex effects, many obstetricians dislike operating on a conscious subject under local infiltration. Both objections can be eliminated with adequate pre-anæsthetic atropine followed by nitrous oxide or ethylene anæsthesia without oxygen lack.

The suitability of spinal anæsthesia for cæsarian section is one of the most controversial questions in anæsthesia. In the past the most authoritative opinions regarded spinal anæsthesia as dangerous in obstetrics. De Lee and Greenhill (1947) and Bourne and Williams (1948) hold definitely to this opinion, and Baird (1950) states that many believe spinal anæsthesia to be dangerous in pregnancy. On the other hand, in this country and in America, a number of anæsthetists are using spinal anæsthesia for cæsarian section with success. Thus, Weintraub and Merrian (1943) reported a series of 345 cæsarian sections performed under spinal anæsthesia without a maternal death, Resnick (1945) 137 cases with no maternal deaths, Thomas (1947) 346 cases without a maternal death and Malkin (1947) 736 cæsarian sections without a maternal death that could be attributed to the spinal anæsthetic.

During spinal anæsthesia, the local anæsthetic used can have no action on the fœtus *in utero*. When a successful spinal anæsthetic is produced to the level of dorsal 11, the blocking of the spinal nerve roots as they cross the subarachnoid space produces

complete loss of sensation and muscle tone in the areas served by these spinal nerves, but uterine tone is unaffected and during cæsarian section excessive uterine tone may occasionally hinder the rapid delivery of the child. As in infiltration anæsthesia, reflex effects produced by emotional stress during spinal anæsthesia can be controlled with atropine and hypnotics or light inhalation anæsthesia; but heavy or ill-timed hypnosis, or too-deep or too-prolonged inhalation anæsthesia will depress the central nervous system of the fœtus, and abolish the principle and perhaps the only material advantage gained when spinal anæsthesia is employed in a pregnant woman at term. In a successful spinal anæsthetic for cæsarian section the new-born babe breathes spontaneously as soon as it is delivered; so far as the fœtus and the anæsthetic preparation are concerned, spinal anæsthesia differs from local infiltration only in the greater freedom of action permitted to the surgeon because of the complete loss of sensation in all the tissues within the operative field. If the possibility of maternal collapse and/or sudden death could be eliminated, no serious objection could be advanced against the use of spinal anæsthesia in pregnant women. It is this maternal risk in spinal anæsthesia, and its consequent danger to the fœtus *in utero*, upon which there is lack of agreement The figures of the observers quoted above indicate (in spite of the small series reviewed) that spinal anæsthesia can be safely used for cæsarian section. The maternal dangers of spinal anæsthesia during pregnancy which have been discussed above apply with even greater force at term. In the writer's opinion, these dangers are sufficiently potent to contra-indicate the use of spinal anæsthesia for cæsarian section or parturition.

The use of caudal anæsthesia is relatively common in institutional obstetric practice in America and has been employed by Galley (1949) and others in this country. It is used occasionally for cæsarian section but is more commonly employed during normal labour—in this connection it will be discussed later.

For many years, blood-borne anæsthetics have been used successfully for cæsarian section. It has been concluded that the administration of a correctly determined combination of blood-borne anæsthetics does not introduce significant maternal risks during pregnancy. Blood-borne anæsthesia to the level of sensory loss relaxes the tone of the uterus, and a slightly deeper level of

anæsthetic depression produces relaxation of the lower abdominal musculature. Hence, as far as maternal safety and the production of an efficient maternal anæsthetic preparation are concerned, a suitable combination of blood-borne anæsthetics provides an ideal method of anæsthetising a subject for cæsarian section. It has been seen that the rate of uptake of blood-borne anæsthetics by the fœtal brain is slow relative to their uptake by the maternal brain. This makes it possible to administer a suitable combination of blood-borne anæsthetics in such a way that maternal risks are insignificant and relaxation of the abdominal and uterine muscles adequate for the delivery of the child before a sufficient time has elapsed for the fœtal brain to absorb an effective concentration of these anæsthetics from maternal blood. In this instance, unless other factors such as fœtal anoxia were acting, the new-born child reacts to external stimulation and breathes spontaneously as soon as it is delivered. If, however, maternal anæsthesia is too deep for too long a time before the child is delivered, its central nervous system will be depressed in keeping with the depth and the duration of maternal anæsthesia before its delivery. It is clear that successful blood-borne anæsthesia for cæsarian section depends upon the individual characteristics of the blood-borne anæsthetics use, the method of their administration, and a close co-operation between the anæsthetist and the obstetric surgeon.

The experience of generations of anæsthetists and obstetric surgeons has shown that a correctly administered combination of nitrous oxide, oxygen and di-ethyl ether can provide maximal maternal safety, an efficient anæsthetic preparation and a babe who breathes spontaneously on or soon after delivery. Since correct administration plays such a large part in the production of satisfactory blood-borne anæsthesia for cæsarian section, the following description is appended. Adequate premedication with atropine is essential to safety but it is wise to omit premedication with morphia and the non-reactive barbiturates, for these agents are excreted slowly and may depress the fœtus. Since the uptake of intravenous barbiturates is rapid, fœtal depression will be produced if evipan or pentothal are used for anæsthetic induction; and if maternal liver inefficiency is present intense fœtal depression is certain and the maternal risk significantly increased. Induction with nitrous oxide and oxygen is begun as soon as the surgeon

and theatre staff are scrubbed up and ready to commence; with the cautious addition of di-ethyl ether, anæsthesia is rapidly carried to the level of complete sensory loss. As soon as anæsthetic control has been achieved, the subject can be cleansed and towelled; by the time this has been completed it is safe for the surgeon to commence operating. By the time the peritoneum is opened, anæsthesia should be deep enough in a classical cæsarian section to allow the uterus to be delivered into the wound and controlling packs inserted; and a similar depth of anæsthesia is required for an efficient controlled exposure in a lower segment cæsarian section. If at this point di-ethyl ether is cut off and anæsthesia continued with nitrous oxide and oxygen, the babe when delivered is found to have absorbed during this period of time insufficient blood-borne anæsthetic to significantly depress its respiratory centre; and in the absence of fœtal anoxia, it breathes spontaneously on or soon after delivery. A similar result is achieved with ethylene, oxygen and di-ethyl ether. If cyclopropane is a suitable anæsthetic for the mother, this anæsthetic—with sufficient di-ethyl ether to produce an efficient surgical exposure without maternal cardiovascular effects—provides greater protection from depression of the fœtal respiratory centre than do nitrous oxide or ethylene and di-ethyl ether, for it is absorbed by fœtal brain, relative to maternal brain, more slowly than nitrous oxide or ethylene. When the fœtus and the placenta have been delivered, muscular relaxation is no longer required because of the reduced size of the emptied uterus and the stretched condition of the abdominal wall, and uterine repair and abdominal closure can be performed at a light level of anæsthetic depression

It is seen that blood-borne anæsthesia sufficient to produce relaxation of abdominal muscles is required during cæsarian section only for a very short time. Pentothal in 2 5 per cent. solution is sometimes used during light blood-borne anæsthesia to produce this short period of relaxation. It is given intravenously just before the uterus is opened if the child is swiftly delivered there is insufficient time for the fœtus to absorb a depressive amount of pentothal, but if unexpected obstetric complications delay delivery, serious fœtal depression may occur. Local infiltration is also employed for this purpose but the time taken (before the fœtus

is delivered) to produce muscular relaxation with infiltration anæsthesia may defeat the end in view, for it increases the time during which the fœtus is exposed to the blood-borne anæsthesia. This objection does not apply when d-tubo-curarine chloride is used for it acts very rapidly. Neither local infiltration nor d-tubo-curarine chloride, however, produce relaxation of the uterine muscle. This effect is produced by anæsthesia to the level of complete sensory loss, which, it has been concluded, is the lightest level of anæsthetic depression capable of protecting the subject from reflex effects. For these reasons inhalation anæsthesia to the level of complete sensory loss is desired during cæsarian section and, since so little additional blood-borne anæsthetic is necessary to produce relaxation of the abdominal muscles for the short time required, it is questionable whether the use of local infiltration or the injection of d-tubo-curarine chloride confers any material benefit.

To the pregnant woman at term the relief of the pains of labour is of paramount importance, but to the obstetrician the relief of pain and the control of the subject are necessary for efficient obstetrics and the maintenance of complete asepsis during parturition. This must be done with safety to the mother and the fœtus, and without interfering with the mechanism of normal labour.

There is no known single cause for the onset of labour and Reynolds (1939) states that "parturition begins as a result of the gradual accelerating convergence of a number of factors, structural, humeral, nervous, nutritional and circulatory." When labour is established, however, the dominant factors acting are structural, humeral and nervous.

Parturition can occur in experimental animals after section of the sympathetic nerve supply to the uterus and after section of the spinal cord in the mid-thoracic region. Atropine, which paralyses para-sympathetic effectors peripherally, does not affect uterine contractions during labour In atropinized women, spinal anæsthesia to the level of the tenth thoracic segment or sacral anæsthesia to a corresponding level, abolishes the pain and does not inhibit the forces of labour: but the forceps rate is high. Hence, the blocking of these posterior spinal nerve roots abolishes the pain of labour, while blocking of the corresponding anterior spinal

effective concentration can readily be absorbed by the cortical areas and hypothalamic nuclei of the brain within this time limit. Beecher (1940) states that it is questionable whether ether and chloroform directly affect the uterus. It is most probable that the reversible inhibition of uterine contractions produced by anæsthetics during labour must be attributed to their central action on the brain. The following observations indicate that, when the anæsthetic depression of the maternal brain is deeper than the level of anæsthetic sleep, uterine contractions cease and the course of labour is halted.

During the second stage of labour, it has been seen that blood-borne anæsthesia accurately maintained at the level of anæsthetic sleep (*Guedel's first plane) does not inhibit uterine contractions* or halt the course of labour and it has been concluded at this level of anæsthesia that the cortical areas and the sympathetic entities (the posterior and lateral nuclei) of the hypothalamus are depressed. As anæsthesia deepens, the anterior and medial hypothalamic nuclei are next depressed; and during the second stage of labour, anæsthesia deeper than anæsthetic sleep arrests uterine contractions and halts the course of labour. During blood-borne anæsthesia deeper than anæsthetic sleep, autonomic and somatic impulses to the uterus are very significantly reduced but observations of the action of spinal and sacral anæsthesia during labour show that the total arrest of autonomic and somatic impulses from the brain and spinal cord does not materially interfere with the mechanism of normal labour. This implies that some function of the anterior and medial nuclei of the hypothalamus, other than the integration of descending effector impulses to the uterus, is concerned with the arrest of uterine contractions which *inevitably* occurs when blood-borne anæsthesia becomes deeper than anæsthetic sleep Fisher *et al* (1938) have shown that pregnant animals with diabetes insipidus produced by hypothalamic lesions have difficulty in delivering their young. In such experimental animals labour may be greatly prolonged, and it may be difficult or even impossible for the uterus to expel its contents. There is reason to believe that the secretion of oxytocin is exclusively under nervous control (it is probably controlled by the supra-optic nuclei of the *medial hypothalamic* group), and that *the failure of the* normal mechanism of labour in these animals is due to the lack

of essential oxytocin hormone. These data suggest that as blood-borne anæsthesia deepens beyond that of anæsthetic sleep the depression of the medial and anterior hypothalamic nuclei (and it is presumed the supra-optic nuclei) not only significantly reduces autonomic and somatic effector impulses to the uterus but also curtails or completely arrests the release of oxytocin. It is therefore probable that blood-borne anæsthesia deeper than the level of anæsthetic sleep arrests the course of parturition by inhibiting in a reversible manner the humeral and nervous factors responsible for labour.

In modern obstetric practice, the relief of pain during labour is in the best interests of the mother and it must be achieved without delaying or halting the normal course of labour, for at term the placental mechanism has almost reached the limit of its physiological reserve and prolongation of labour might well jeopardise the safety of the yet unborn fœtus

During the first stage of labour, which lasts from the commencement of labour pains until the cervix is fully dilated, it is usually sufficient to dull sensibility and produce a state of amnesia and this state of light hypnosis will be recognised as the stage of co-operative stupor. The anæsthetist is seldom present during the first stage of labour, for his advice or service is rarely required. It is only in an especially nervous, unbalanced mother, or when a state of non-cooperative stupor develops after too heavy hypnosis, that excessive and exaggerated emotional and physical stress calls for the services of an anæsthetist. Hypnosis during the first stage of labour is thus the particular province of the obstetrician and it is right that this should be so. No one is more conscious of the needs of the particular mother and the disabilities of too-heavy hypnosis during this stage of labour than the obstetrician himself. But it will not be presumptuous to emphasise the difficulties and dangers that may occur.

In this country, non-volatile anæsthetics such as chloral hydrate with potassium bromide, morphia, pethidine, scopolamine and omnopon and the non-reactive barbiturates and the volatile anæsthetics, nitrous oxide, trichlorethylene and chloroform with air, are commonly used by the obstetrician during the first stage of labour. A rapidly acting hypnotic is desired for primiparæ who approach their first experience of labour with some degree of

trepidation or dread. Since, in primiparæ moreover, the first stage of labour lasts for about fourteen hours and the second stage about two and a half hours, there can be no objection to the use of a hypnotic whose rate of excretion is slow and whose duration of action is relatively prolonged. In multiparæ the first stage of labour is much shorter and the second stage lasts for about 40 to 60 minutes. In multiparæ a hypnotic to be of real use should therefore act rather quickly and the rate of its excretion should be relatively rapid unless the hypnotic administered in the first stage of labour is not to depress the respiratory centre of the new-born babe. Reference to Table 41 shows the characteristic rate of response and excretion of the non-volatile anæsthetics in common clinical use, and it provides a basis for their use in the particular obstetric case and is an indication of the limitations of this form of hypnosis. It must also be remembered that the systemic diseases associated with pregnancy modify the excretory rate of these non-volatile anæsthetics. Thus, the rate of excretion is delayed and the duration of action of predominantly non-reactive anæsthetics—such as the members of the first group of Table 41, and codein and heroin—are materially increased when renal inefficiency is present, the same result will occur with predominantly reactive anæsthetics—such as the members of the third group and morphia and scopolamine—if liver inefficiency is present. Moreover when renal and/or liver inefficiency is present, repeated dosage of these hypnotics will lead to their accumulation with consequent over-dose. Repeated dosage with chloral hydrate in addition may lead to cardiac effects.

Chloroform, trichlorethylene and nitrous oxide are used during the first stage of labour to control pain of uterine contractions. These anæsthetics with air are administered intermittently with each labour pain to produce anæsthesia to the level of co-operative stupor Relative to the non-volatile anæsthetics, the uptake and excretion of these volatile anæsthetics is rapid and the mother recovers between pains. This is especially so with the use of nitrous oxide and air, but if chloroform and particularly trichlorethylene are administered intermittently for very long periods of time, they may accumulate in the tissues. Unless this possibility is realised, chloroform and trichlorethylene anæsthesia may become deep enough to arrest uterine contractions even when anæsthesia

is administered with a machine set to deliver an anæsthetic atmosphere of constant composition. Such accumulation with chloroform or trichlorethylene may predispose to even greater danger, for when overpressure is used with chloroform or trichlorethylene to control a pain rapidly, or to control the violent storm of pains which occasionally occurs, maternal primary cardiac failure may be produced more readily if such accumulation is present. Acute diffuse necrosis of the liver occasionally occurs after chloroform, and nowadays chloroform is contra-indicated because of the possibility of the primary cardiac failure and liver necrosis which may follow its use. Trichlorethylene does not produce liver necrosis, but the maternal fatalities that have occurred since its introduction in 1941 indicate that the danger of primary cardiac failure with this anæsthetic is not sufficiently realised. Nitrous oxide produces neither primary cardiac failure nor liver necrosis but, if anoxia is permitted to act during nitrous oxide anæsthesia, secondary cardiac failure may occur. The only danger with nitrous oxide is that of maternal anoxia; moreover, with nitrous oxide and air it is impossible to produce anæsthesia deeper than the level of co-operative stupor. Hence, if anoxia is avoided with nitrous oxide and air, it is impossible to depress uterine contractions during the first stage of labour, and maternal and fœtal dangers are nil The only objection to self-administered nitrous oxide and air in the first stage of labour is its inability in certain subjects to produce anæsthesia to the level of co-operative stupor and so relieve the pains of labour. It is seen at its best when combined with light hypnosis produced by the non-volatile anæsthetics discussed above. If the dose of these agents or any combination of them is nicely judged for the particular mother, pain, apprehension and nervousness are controlled and labour may be accelerated without harm to the mother or fœtus

As uterine contractions become more frequent and intense with the onset of the second stage of labour, these hypnotics may fail to control pain; in all primiparæ, and in some multiparæ, a deeper level of anæsthetic depression is required to abolish pain and maintain obstetric control during the second stage of labour. Freedom from pain and maintenance of obstetric control, without interference with the normal course of labour, are usually obtained with inhalation anæsthesia to the level of anæsthetic sleep

(Guedel's first plane) but spinal, sacral or infiltration anæsthesia is used occasionally. Nitrous oxide and oxygen anæsthesia is most commonly used during this stage of labour. Because the deepest level of anæsthetic depression that can be produced, in the absence of anoxia, with nitrous oxide is that of anæsthetic sleep, it is impossible to inhibit the normal course of labour with this anæsthetic if anoxia is avoided throughout. But it is difficult to use effectively and for this reason, sufficient di-ethyl ether or trichlorethylene is *often added in order to achieve the level of anæs*thetic sleep without anoxia. The addition of this minimal amount of di-ethyl ether does not increase maternal or fœtal risks. Trichlorethylene, alone or combined with nitrous oxide and oxygen, has become popular with some anæsthetists. Baird (1950) says that trichlorethylene is closely allied to chloroform and carries with it almost the same risks, and this opinion coincides with the conclusions reached in this discussion. He states that the reports to date are on the whole favourable, but it is the writer's opinion that an anæsthetic which can produce primary cardiac failure with overpressure should never be used when it is possible to substitute *one which produces the standard sequence of anæsthetic response.* Anæsthesia to the level of anæsthetic sleep can be readily produced and accurately maintained with ethylene which is slightly more potent than nitrous oxide and ethylene and oxygen in a closed system of breathing might be used with advantage during the second stage of labour If the mother is a suitable subject, an experienced anæsthetist can produce and accurately maintain the level of anæsthetic sleep with cyclopropane and oxygen. In inexperienced hands anæsthesia deeper than anæsthetic sleep may readily be produced and the course of labour halted with cyclopropane, and, if overpressure is used, maternal cardiovascular *distress and/or primary cardiac failure may occur.* Ethyl chloride and di-vinyl ether are seldom used in obstetrics, for their volatility and potency make it difficult to avoid anæsthesia deeper than anæsthetic sleep, moreover, di-vinyl ether may produce liver necrosis in the post-anæsthetic period. Chloroform is contra-indicated because of the danger of primary cardiac failure during anæsthesia and liver necrosis in the post-anæsthetic period. Nitrous oxide and trichlorethylene are non-inflammable. Di-ethyl ether, ethylene and cyclopropane may explode under suitable conditions but if

they are used in a closed system of breathing this danger is eliminated.

If anoxia is avoided throughout, nitrous oxide and ethylene are the safest and most satisfactory inhalation anæsthetics during the second stage of labour, for in the absence of anoxia it is difficult with ethylene, and impossible with nitrous oxide, to produce anæsthesia deeper than the level of anæsthetic sleep and the course of normal labour is not halted. Moreover, their rapid excretion from maternal blood between pains and their relatively slow uptake by fœtal brain combine to make anæsthetic depression of the new-born babe a rare event. Hence, it can be said that maternal and fœtal risks are not increased during the second stage of labour when nitrous oxide or ethylene is used without anoxia. When obstetric complications require a level of depression deeper than anæsthetic sleep, this can be rapidly and safely produced during nitrous oxide or ethylene anæsthesia by the addition of di-ethyl ether.

Local anæsthetics are used less frequently than inhalation anæsthetics in obstetric practice. Local infiltration during labour is the special province of the obstetric surgeon. Enough has been said of the contra-indications to the use of spinal anæsthesia during pregnancy and for cæsarian section to indicate the maternal dangers of this form of anæsthesia during labour. Caudal anæsthesia has proved to be a safe and efficient form of anæsthesia in institutional obstetric practice, for Hingson (1949) reported 12,000 cases of continuous caudal anæsthesia during labour with only two maternal deaths—both being secondary to sepsis in the sacral region. In this form of anæsthesia, the local anæsthetic solution is injected into the peridural space in single or divided dosage through an 18 - 20 bore malleable stainless steel needle or No. 4 - 5 ureteric catheter inserted through the sacral hiatus. It is imperative to ensure that the needle or catheter does not enter the subarachnoid space. A trial dose of 10 c c. of the local anæsthetic solution is slowly injected ; if it enters the peridural space, saddle anæsthesia is established in about ten minutes with 1·5 per cent. metycaine or 1 per cent. procaine. About 30 c.c. of the solution is then injected slowly. Within about ten minutes anæsthesia is established to the level of dorsal 11, and the pain of uterine contractions has disappeared. Relief from pain lasts from

(Guedel's first plane) but spinal, sacral or infiltration anæsthesia is used occasionally. Nitrous oxide and oxygen anæsthesia is most commonly used during this stage of labour. Because the deepest level of anæsthetic depression that can be produced, in the absence of anoxia, with nitrous oxide is that of anæsthetic sleep, it is impossible to inhibit the normal course of labour with this anæsthetic if anoxia is avoided throughout. But it is difficult to use effectively and for this reason, sufficient di-ethyl ether or trichlorethylene is often added in order to achieve the level of anæsthetic sleep without anoxia. The addition of this minimal amount of di-ethyl ether does not increase maternal or fœtal risks. Trichlorethylene, alone or combined with nitrous oxide and oxygen, has become popular with some anæsthetists. Baird (1950) says that trichlorethylene is closely allied to chloroform and carries with it almost the same risks, and this opinion coincides with the conclusions reached in this discussion. He states that the reports to date are on the whole favourable, but it is the writer's opinion that an anæsthetic which can produce primary cardiac failure with overpressure should never be used when it is possible to substitute one which produces the standard sequence of anæsthetic response. *Anæsthesia to the level of anæsthetic sleep can be readily produced* and accurately maintained with ethylene which is slightly more potent than nitrous oxide and ethylene and oxygen in a closed system of breathing might be used with advantage during the second stage of labour. *If the mother is a suitable subject, an* experienced anæsthetist can produce and accurately maintain the level of anæsthetic sleep with cyclopropane and oxygen. In inexperienced hands anæsthesia deeper than anæsthetic sleep may readily be produced and the course of labour halted with cyclopropane, and, if overpressure is used, maternal cardiovascular distress and/or primary cardiac failure may occur. Ethyl chloride and di-vinyl ether are seldom used in obstetrics, for their volatility and potency make it difficult to avoid anæsthesia deeper than anæsthetic sleep; moreover, di-vinyl ether may produce liver necrosis in the post-anæsthetic period. Chloroform is contra-indicated because of the danger of primary cardiac failure during anæsthesia and liver necrosis in the post-anæsthetic period. Nitrous oxide and trichlorethylene are non-inflammable. Di-ethyl ether, ethylene and cyclopropane may explode under suitable conditions but if

which she may be suffering, and to the fœtus which is soon to commence an independent existence. It would appear that these conditions can be fulfilled by an efficient anæsthetist using each and every method of anæsthesia that has been discussed. An anæsthetist who is both skilful and experienced is not always available for obstetric work; moreover, during anæsthesia it is not enough to provide only for the subject whose reaction is the standard one. Absolute maternal safety—and this implies safety for the unborn fœtus—is achieved only if the anæsthetic methods adopted provide for the uncommon and occasional complications that may occur in a pregnant woman at term. It is the writer's experience that the most controllable form of anæsthesia—inhalation anæsthesia — gives the greatest measure of maternal protection in all circumstances, if the combination of volatile anæsthetics chosen for the particular subject is varied in the manner discussed in accordance with her clinical condition. When antenatal care has been inadequate or when one of the systemic disorders of pregnancy is present, some degree of maternal protein depletion and/or liver disfunction is likely to be present. In such subjects, the pre-anæsthetic use of methionine is an obvious prophylactic measure and if chloroform or di-vinyl ether has been used, Whipple's observations indicate that it would be an omission bordering on clinical negligence, to fail to use methionine therapy in the immediate post-anæsthetic period.

The resuscitation of the new-born babe usually falls to the lot of the anæsthetist. In the absence of the developmental errors and birth injuries, the central nervous system of the new-born babe can be depressed only by anoxia and/or blood-borne anæsthesia. Of these two factors, oxygen lack is the most potent and dangerous depressant and its action may be irreversible. It is also the factor that can be most rapidly abolished Moreover, a volatile blood-borne anæsthetic cannot be excreted from the blood of the infant unless and until effective lung ventilation is established, and the rate of detoxication and/or excretion of non-volatile anæsthetics is retarded if anoxia reduces the circulatory rate. It is imperative first to abolish anoxia, and after clearing the naso-pharynx of secretion, this is done by insufflating the babe with an oxygen atmosphere by gentle rhythmic pressure on the oxygen bag, which

forty-five to sixty minutes: so long as the second stage of labour persists, 20 c.c. of the anæsthetic solution are injected every forty minutes. An admirable description of the technique of administration of caudal anæsthesia is given by Galley (1949). Caudal anæsthesia is contra-indicated by the presence of infection round the site of the sacral hiatus and is unsuitable in nervous, un-co-operative mothers. It must not be begun until the cervix is dilated to about 5 cm. and it takes about thirty minutes to establish anæsthesia. Hingson states that caudal anæsthesia prolongs labour in one-third of cases, and apparently hastens labour in a similar percentage; but the duration of the *second* stage of labour is definitely increased in all cases. Hypotension occurred in 22 per cent. of cases and was corrected with posture, vasopressor drugs and intravenous fluids. Galley states that during caudal anæsthesia nerve fibres are blocked in the same order as, but more slowly than, during spinal anæsthesia. The freedom from maternal cardiovascular calamities characteristic of spinal anæsthesia can be attributed (1) to the low level of nerve block, viz. 11th dorsal, and (2) to the slower onset of anæsthesia, which possibly allows a greater time for the heart to compensate for the field of peripheral resistance paralysed. The greatest danger is the inadvertent injection of the solution into the subarachnoid space. Hingson states that sepsis round the site of injection occurs once in every 1,000 caudal anæsthetics. With caudal anæsthesia the forceps rate is high and, since this form of anæsthesia does not relax uterine muscle, intra-uterine manipulations under caudal anæsthesia are impossible But in his 12,000 caudal anæsthetics, Hingson had only two maternal deaths and the overall infant mortality, relative to controls, was reduced by half. Hence, in suitable subjects, pain is abolished and the danger to mother and fœtus is reduced to minimal proportions. There can be little doubt that if an experienced anæsthetist is available caudal anæsthesia has much to recommend it for institutional obstetrics

When an anæsthetic is required for a woman at term, for either cæsarian section normal labour, this discussion indicates that the anæsthetist must lfil a number of essential conditions. The maternal anæsthetic paration must meet the needs of the obstetric surgeon, and is end must be achieved with absolute safety to the mother, ha) regard to the systemic disorders from

temperature shows diurnal variation. It is lowest early in the morning between the hours of 5 A.M. and 8 A.M. and is highest in the evening. This normal variation of body temperature is due to muscular activity during the hours of daylight; the temperature curve is reversed in healthy night workers. The temperature curve of babies is at first irregular and then becomes periodic as regular habits of rest and exercise are acquired; but in infants, small effects may produce gross alterations of body temperature. Generally speaking the body temperature of old people is subnormal and they respond sluggishly to changes in their external environment, for their circulation is relatively feeble and they are less active. The skin temperature varies in different parts of the body and should it become uniform throughout the body, intense discomfort results. Moreover, Bazett *et al.* (1948) have shown by means of thermocouples inserted into superficial veins and into the brachial, the radial and the common iliac arteries, that the temperature of circulating blood varies within wider limits than was hitherto supposed. In a cold environment, the blood temperature in the superficial veins of the wrist and forearm is much lower, the more distal the point of measurement; in a hot environment the temperature gradient is apt to be reversed. The temperature of circulating blood was found to vary in different arteries, and significant fluctuations of temperature were produced in the blood of a given artery by cooling of the body distal to the site of measurement. This cooling of arterial blood was observed to depend upon the re-warming of cold venous blood returning from more distal areas in veins adjacent to the artery. Variations of the order of 0 3 degrees Centigrade were observed in the brachial artery, and temperatures as low as 21·5 degrees Centigrade in the radial and 31 1 degrees Centigrade in the brachial artery were produced without the subject complaining unduly of cold in the upper extremity, and without producing a particularly low rectal temperature. The temperature in the rectum and in the brachial and the common iliac arteries may differ significantly from one another; responding to external thermal stimulation, each undergoes temperature changes of a different magnitude with greatly different degrees of time lag. The conception of a uniform blood temperature throughout the whole body of Man must therefore be abandoned, but there is no reason to doubt that metabolism

is attached to a face-piece, or to an endotracheal catheter introduced on the finger or by direct vision, after the method of Blaikley and Gibberd (1935). Since fœtal anæsthesia is seldom sufficient completely to depress the respiratory centre of the new-born babe, and because, as Barcroft (1946) has shown in sheep, oxygen is a potent stimulant to the fœtal respiratory centre, the completely oxygenated infant soon commences to breathe spontaneously. Even if the infant does not now breathe spontaneously, it is pink and safe. Its cardiovascular system soon returns to normal and will remain so as long as it is adequately oxygenated in this manner. Moreover, the detoxication and/or excretion of non-volatile anæsthetics and the deviation of volatile anæsthetics to non-nervous tissue are accelerated as the circulatory rate increases. The anæsthetic concentration in the respiratory centre consequently falls and the infant begins to breathe spontaneously. At first, breathing consists of isolated gasps, which are followed by quiet shallow breathing. At length the infant cries, at first feebly and then lustily; from this time onwards the excretion of volatile anæsthetics is rapid. It is seldom necessary to add carbon dioxide to the oxygen atmosphere insufflated, for, in the absence of lung ventilation, the babe is thought to contain an abundance of carbon dioxide. Carbon dioxide stimulates the respiratory centre and the nerve endings in the nasopharynx and larynx; it is observed in clinical practice that the insufflation of an oxygen atmosphere containing about 6 - 10 per cent. of carbon dioxide does help to establish spontaneous respiration. When respiratory depression occurs in a new-born babe the anæsthetic factor is seldom if ever dangerous if the anoxia is quickly abolished; but when these two factors are allowed to act synergically for a length of time that depends upon the vitality of the particular infant, secondary cardiac failure soon produces death.

Body Temperature. Man is a homoiothermic subject, and when exposed to extremes of environmental change has the ability to maintain his body temperature within definite physiological limits. The range of oral temperature in a healthy man is 96·7 - 99 degrees Fahrenheit but the rectal temperature, a more reliable index of body temperature, is higher and lies between 97 2 and 99 5 degrees Fahrenheit. In a healthy subject the body

temperature shows diurnal variation. It is lowest early in the morning between the hours of 5 A.M. and 8 A.M. and is highest in the evening. This normal variation of body temperature is due to muscular activity during the hours of daylight; the temperature curve is reversed in healthy night workers. The temperature curve of babies is at first irregular and then becomes periodic as regular habits of rest and exercise are acquired; but in infants, small effects may produce gross alterations of body temperature. Generally speaking the body temperature of old people is sub-normal and they respond sluggishly to changes in their external environment, for their circulation is relatively feeble and they are less active. The skin temperature varies in different parts of the body and should it become uniform throughout the body, intense discomfort results. Moreover, Bazett *et al.* (1948) have shown by means of thermocouples inserted into superficial veins and into the brachial, the radial and the common iliac arteries, that the temperature of circulating blood varies within wider limits than was hitherto supposed. In a cold environment, the blood temperature in the superficial veins of the wrist and forearm is much lower, the more distal the point of measurement; in a hot environment the temperature gradient is apt to be reversed. The temperature of circulating blood was found to vary in different arteries, and significant fluctuations of temperature were produced in the blood of a given artery by cooling of the body distal to the site of measurement. This cooling of arterial blood was observed to depend upon the re-warming of cold venous blood returning from more distal areas in veins adjacent to the artery. Variations of the order of 0 3 degrees Centigrade were observed in the brachial artery, and temperatures as low as 21 5 degrees Centigrade in the radial and 31 1 degrees Centigrade in the brachial artery were produced without the subject complaining unduly of cold in the upper extremity, and without producing a particularly low rectal temperature. The temperature in the rectum and in the brachial and the common iliac arteries may differ significantly from one another; responding to external thermal stimulation, each undergoes temperature changes of a different magnitude with greatly different degrees of time lag. The conception of a uniform blood temperature throughout the whole body of Man must therefore be abandoned, but there is no reason to doubt that metabolism

in the vital internal organs is most efficient at a certain mean temperature and that the body temperature in health is maintained within the limits quoted above.

The regulation of body temperature is accomplished by the calorific balance achieved between heat production within the body and heat loss from the body.

Heat production depends upon the metabolic rate of the body. The index employed to describe the heat production of a particular subject is his resting or basal metabolic rate (B.M.R.). In an average healthy subject, it is one large calorie per kilo of body weight per hour. This is equivalent to the heat required to raise the temperature of one kilo of water from 15 to 16 degrees Centigrade, and in the process 4185×10^7 ergs are changed into heat. This index is closely related to the surface area of the subject and, in a lesser degree, to his height and weight. In normal conditions of life, the B.M.R. of a healthy adult may vary by $\pm$ 10 per cent. In an adult with a surface area of 1 8 square metres, the B.M.R. of males is 40 calories and that of females 37 calories per square metre per hour. The heat produced by a new-born babe per kilo of body weight in the first twenty-four hours of life is about the same as an adult, but its surface area relative to its body weight is larger and it has a lower B.M.R. Premature infants at birth and for several months afterwards have a lower metabolic rate than full-term infants It is stated that heat production in the tropics is 10 per cent. lower and in frigid zones about 33 per cent. higher than the normal for temperate zones

The principle source of body heat is the metabolic processes of the body. A proportion of the energy liberated during metabolism is used to make good the wear-and-tear on, and to maintain the activities of, the vital organs—heart, brain, glands, etc.—but the greater part of this energy is converted into body heat During voluntary muscular activity, oxygen consumption may increase from the basal requirements of about 250 c.c. per minute to 4 - 4½ litres per minute, representing a sixteen- or eighteen-fold increase in the metabolic rate, with a corresponding rise in body heat production. Reflex stimulation of metabolism occurs when, in the absence of voluntary activity, the skin is exposed to cold Swift (1932) and most other observers attribute this increased production of heat to the involuntary muscular activity of

shivering. In Man, shivering commences when the skin temperature falls to about 19 degrees Centigrade, and heat production may increase as much as 18 per cent. above normal; at an external temperature of 2 degrees Centigrade intense shivering may increase body heat production by 400 per cent. A short exposure to a rise of temperature in the external environment has little effect in Man, but prolonged exposure to a high temperature is followed by a gradual diminution of the metabolic rate; and heat production decreases during natural sleep and prolonged rest.

The ductless glands play an important rôle in the increased metabolic rate which follows voluntary or involuntary muscular activity. Thyroid secretion is a general metabolic catalyst and each additional milligram entering the blood stream increases metabolism by 1000 calories. In Graves' disease the metabolic rate may be increased by 100 per cent. while in myxœdema it may be decreased by 50 per cent. Metabolism is also influenced by the pars anterior of the pituitary which regulates thyroid secretion, and a metabolic hormone has been extracted from the pars anterior and intermedia which increases the rate of tissue oxidation locally. Adrenaline produces a transitory rise of metabolism of about 20 per cent. for a period of about twenty minutes.

In addition to supplying energy, the greater part of which is converted into heat, food, *per se*, stimulates metabolism and so is a direct source of body heat. When a subject is given 1800 calories of food in a mixed diet over a period of 24 hours, nearly 2000 calories of body heat are produced. The extra 200 calories of heat over and above the calorific value of the food ingested is not accounted for by digestion, absorption, the activity of muscles, glands, etc., and is attributed to the drug-like stimulation of the fatty acid residue which remains after the NH_2 groups have been removed from amino acids. This excess of heat production is termed *the specific dynamic action* of the particular foodstuff and amounts to 30 per cent. in the case of proteins, 4 per cent. for fats and 4 - 6 per cent. in the case of carbohydrates. The specific dynamic action of food stimulates the metabolic rate while starvation and prolonged vegetarianism (five years and longer) results in a low metabolic rate.

Heat production is increased in certain pathological states, such

in the vital internal organs is most efficient at a certain mean temperature and that the body temperature in health is maintained within the limits quoted above.

The regulation of body temperature is accomplished by the calorific balance achieved between heat production within the body and heat loss from the body.

Heat production depends upon the metabolic rate of the body. The index employed to describe the heat production of a particular subject is his resting or basal metabolic rate (B.M.R.). In an average healthy subject, it is one large calorie per kilo of body weight per hour. This is equivalent to the heat required to raise the temperature of one kilo of water from 15 to 16 degrees Centigrade, and in the process 4185 × 10^7 ergs are changed into heat. This index is closely related to the surface area of the subject and, in a lesser degree, to his height and weight. In normal conditions of life, the B.M.R. of a healthy adult may vary by ± 10 per cent. In an adult with a surface area of 1 8 square metres, the B.M.R. of males is 40 calories and that of females 37 calories per square metre per hour. The heat produced by a new-born babe per kilo of body weight in the first twenty-four hours of life is about the same as an adult, but its surface area relative to its body weight is larger and it has a lower B.M.R. Premature infants at birth and for several months afterwards have a lower metabolic rate than full-term infants. It is stated that heat production in the tropics is 10 per cent. lower and in frigid zones about 33 per cent. higher than the normal for temperate zones.

The principle source of body heat is the metabolic processes of the body. A proportion of the energy liberated during metabolism is used to make good the wear-and-tear on, and to maintain the activities of, the vital organs—heart, brain, glands, etc.—but the greater part of this energy is converted into body heat. During voluntary muscular activity, oxygen consumption may increase from the basal requirements of about 250 c.c. per minute to 4 - 4½ litres per minute, representing a sixteen- or eighteen-fold increase in the metabolic rate, with a corresponding rise in body heat production. Reflex stimulation of metabolism occurs when, in the absence of voluntary activity, the skin is exposed to cold. Swift (1932) and most other observers attribute this increased production of heat to the involuntary muscular activity of

per cent. from the lungs and 14·7 per cent. from the skin surface while the remaining 5 per cent. is lost in the excreta.

The efficiency of each of these physical processes as a means of heat loss depends almost entirely upon the environment to which the body is exposed. Heat loss by radiation can occur when the body temperature is higher than its external environment, and the greater the temperature gradient between these two systems the greater will be the heat lost by radiation. While radiation is the greatest responsible factor in heat loss, it is relatively inflexible, for heat lost by radiation increases by only 15 Calories per hour for each degree Centigrade rise of the skin temperature above normal. In like manner, heat loss by conduction and convection occurs only when the body temperature is higher than that of the environment to which the body is exposed, and moist air is a better conductor than dry air.

When the temperature of the external environment is greater than that of the body, heat loss can occur only by the evaporation of water on the skin surface and in the lungs, and this in turn is related to the temperature and the humidity of the atmosphere to which the body is exposed. Thus, in a dry room at a temperature of 240 - 260 degrees Fahrenheit the heat lost, mainly by evaporation of water on the skin surface, is sufficient to maintain a normal rectal temperature. On the other hand, exposure for fifteen minutes in a moist room at 130 degrees Fahrenheit produced a rise of body temperature to 100 degrees Fahrenheit; and if the atmosphere is saturated with water vapour at body temperature, heat loss by evaporation at the skin surface is difficult and excretion of water vapour by lung ventilation impossible. Air movement is an important aid to the evaporation of water on the skin surface. In still air, when the wet bulb is above 85 degrees Fahrenheit the rectal temperature may rise; when air movement equivalent to 50 metres per minute is produced in the atmosphere, no rise of rectal temperature occurs with a wet bulb as high as 93 degrees Fahrenheit.

Body water plays an important rôle in the regulation of body temperature. The high thermal conductivity of water produces the rapid equalization of heat throughout the body and its high specific heat favours heat storage by the body. On the other hand, loss

as fevers. For every 1 degree Fahrenheit rise of body temperature, the metabolic rate is increased by 7 per cent. and when during a disease such as pneumonia, typhoid fever, malaria etc. the body temperature rises to 105 degrees Fahrenheit, the metabolic rate is increased by 50 per cent. It is thought that the toxic destruction

TABLE 63

LOSS OF HEAT FROM THE BODY.

(Burns [1921].)

Sources of heat loss from the body	%	Calories per day
Radiation	60 0	1792
Conduction and convection	13 0	—
Evaporation—		
Lungs	7 3	182
Skin	14 7	164
Excreta—		
Carbon dioxide	3 0	84
Urine and fæces	2 0	48
Total heat loss per day	100	2270

of protein is responsible for the increased metabolic rate, but it is not known definitely whether the temperature of the fevers is the cause or the result of increased katabolism. The metabolic rate is also increased to the same order as in Graves' disease during splenomedullary and lymphatic leukæmias. A less marked increase is observed in pernicious anæmia and in uncompensated heart disease, but no explanation has as yet been offered for this phenomenon.

The mechanism of the regulation of heat loss from the body is sometimes called the physical regulation of body heat, for in resting conditions it depends almost entirely upon physical phenomena The physical processes employed are seen in Table 63 and in a resting subject it is seen that radiation is responsible for 60 per cent. of the heat lost, conduction and convection for 13 per cent , evaporation for 22 per cent in the proportion of 7 3

soles and the axillæ, but in extreme instances may occur over the whole skin surface.

Man is a homoiothermic subject. In the presence of environmental change of considerable range, he has the ability to regulate such a delicate balance of heat production and heat loss that his body temperature is maintained within normal physiological limits

When a subject, lying perfectly still, sufficiently long after his last meal to ensure that digestion has ceased, is exposed to an environment of constant humidity whose temperature lies between 30 and 35 degrees Centigrade, those factors that increase heat production — namely, emotional stress, muscular activity, extremes of external temperature, digestion and the specific dynamic action of food—are reduced to minimal proportions, and the metabolism of the subject and in turn his heat production are reduced to a basal level. Under these standard conditions of basal heat production and external environment, the physical mechanism of heat loss—namely, radiation, conduction, convection, invisible perspiration and its evaporation, the excretion of water vapour in expired air, and heat loss in excreta—strikes an accurate calorific balance between basal heat production and heat loss, and maintains the body temperature within the normal physiological limits quoted above. Should emotional and physical stress rapidly increase heat production, these physical factors are an inadequate means of promoting sufficient heat loss to prevent a rise of body temperature and heat loss is rapidly augmented to meet this state of emergency by an increased elimination of water from the body; for, in these conditions, the minute volume of lung ventilation is increased, dilatation of the skin capillaries increases the volume of invisible perspiration, and sweating commences. Although an increase of breathing and invisible perspiration are valuable means of augmenting heat loss, they soon reach the limit of their usefulness. On the other hand, the volume of sweat secreted on the skin surface may increase to between 1 and 2 litres per hour, and sweating is the most flexible and important means of regulating heat loss in the face of excessive heat production. These effects, which are under the control of the central nervous system, result in the rapid loss of considerable heat by the body, not only because of the high specific heat of water but also because of its subsequent evaporation on the skin surface.

of water by the body provides a rapid and a ready means of heat loss. Moreover, the evaporation of water on the skin surface, which occurs at all temperatures and increases with rise of body temperature, permits a large and rapid heat loss, for the latent heat of evaporation of water is high. Hence, water excretion and its evaporation on the skin surface provides a large and a flexible means of promoting heat loss, and the water vapourised on the skin surface is obtained from two distinct and separate sources.

At a resting metabolic rate, 600 - 800 c.c. of water diffuse from the tissue spaces through the whole skin surface each twenty-four hours. This water is called *insensible perspiration*. It increases slightly when the blood flow through the skin is increased and with a rise in the temperature of the atmosphere to which the body is exposed, but its volume is slightly diminished when the humidity of the atmosphere is increased. The loss of water vapour in expired air is exactly analogous to insensible perspiration, for water vapour diffuses from blood flowing in the pulmonary capillaries through the respiratory membrane to alveolar air to be excreted with the next expiration. When the blood flow through the lungs and the volume of lung ventilation are increased, there follows an increased excretion of water vapour in expired air: but if inspired air is saturated with water vapour at body temperature, the excretion of water vapour by the lungs is difficult. In a resting man, the water lost in twenty-four hours by lung ventilation amounts to between 300 and 400 c.c. which is about half the volume of insensible perspiration during the same period, and the total amount of water lost by diffusion from the skin and the pulmonary system is about 900 - 1200 c.c. in twenty-four hours.

The sweat glands provide the second source of water available for evaporation on the skin surface. Sweat is a watery liquid containing urea, 0·1 - 0·9 per cent. of sodium chloride and, during exercise, sodium lactate. The secretion of sweat is related to blood temperature, which rises when there is increased heat production and/or insufficient heat loss by physical means, and the secretion of sweat then begins. This type of sweating, called *thermal sweating*, is generalized over the whole body and is a very successful temporary expedient to deal with an excessively rapid rise of body temperature. Sweating may also be produced by emotional stress; as a rule, emotional sweating is limited to the palms, the

of a series of subjects was compared before and one hour after adequate premedication with scopolamine and omnopon or morphia and atropine, no change was observed in 45 per cent. of cases; in 43 per cent. of cases it was higher and in 12 per cent. of cases it was lower than the mouth temperature prior to premedication. The average range of temperature change was of the order 0·9 degrees Centigrade.

Moore (1918) demonstrated that merely tying a rabbit to a board in the supine position produced a fall of body temperature of 1 - 2 degrees Centigrade, followed after a stationary period by a rise of body temperature to 0·5 degrees Centigrade above normal. Wright (1942) states that when a man at rest is completely insulated so that he neither loses heat to nor gains heat from the exterior it is found that his body temperature rises by about 2 degrees Centigrade per hour, simply owing to retention of the heat liberated from normal resting metabolism. Since heat production after premedication is at a basal level, these data indicate that a rise of body temperature after premedication must be attributed to insufficient heat loss, while a fall of body temperature during this period is due to excessive heat loss. The following observations indicate the factors acting in each instance.

In India, at a hospital on the plain at an altitude of less than 600 feet, the problem during the hot humid season of the year was to keep cool. Factors promoting heat loss by physical means were encouraged, clothes were reduced to the scantiest proportions and fans were used to promote air movement. In these conditions, although the nervous mechanism of heat loss was relatively depressed by premedication, it was observed that the body temperature rose after premedication in only 27 per cent. of cases, it fell in 17 per cent., and no change was observed in 55 per cent. of cases The maintenance of a normal body temperature in more than half and a rise of body temperature in only 27 per cent. of subjects indicate the success of the positive measures adopted to ensure that heat loss by physical means was adequate These results are in contrast to the high incidence of heat stroke in alcoholics in this environment. These stuporosed subjects often failed to remove their clothes and/or to turn on their fan before falling asleep. This failure to take the elementary measures necessary to promote maximal heat loss by physical means,

The regulation of body temperature is represented at each level of the central nervous system from the cerebral cortex to the spinal cord. For example, sweating is produced by direct reflex stimulation of centres in the cerebral cortex, in the hypothalamus, in the medulla and in the spinal cord.

Benedict (1915) and others have shown that the heat production of a healthy subject is reduced to 13 - 20 per cent. below the basal level during natural sleep. During a properly conducted anæsthetic, when emotional and physical stress is avoided by adequate premedication and a swift and trouble-free induction, the activity of muscles, glands and other forms of heat production is reduced, and during anæsthesia to the stage of anæsthetic sleep or deeper, it can be assumed that the level of heat production corresponds to that of natural sleep and may even be reduced below this level.

For the purpose of this discussion, heat loss can be divided into the purely physical mechanism of heat loss—which depends in the main upon the temperature, the humidity and the air movement of the atmosphere to which the subject is exposed—and those factors such as sweating, vasodilatation and increased lung ventilation, which are under the direct control of the central nervous system They will be referred to below as the physical and the nervous mechanisms of heat loss. During anæsthesia, when a properly clothed subject is exposed to a constant environment, there is no reason to suppose that the physical mechanism of heat loss is modified in a significant degree, but it is probable that the efficiency of the nervous mechanism of heat loss will be materially curtailed because of the anæsthetic depression of the central nervous system It can be expected therefore that the delicately co-ordinated mechanism of heat regulation will be modified during anæsthesia as heat production is reduced to a basal level or less, and as the nervous control of heat loss becomes less flexible with the progressive anæsthetic depression of the cerebral cortex and in turn the hypothalamus

During the degree of hypnosis produced by adequate anæsthetic premedication, the cortical areas of heat control are in a measure depressed The subject is at rest, heat production is at a basal level and the nervous control of heat loss is less flexible than in normal conditions of life. Thus, when the mouth temperature

of a series of subjects was compared before and one hour after adequate premedication with scopolamine and omnopon or morphia and atropine, no change was observed in 45 per cent. of cases; in 43 per cent. of cases it was higher and in 12 per cent. of cases it was lower than the mouth temperature prior to premedication. The average range of temperature change was of the order 0·9 degrees Centigrade.

Moore (1918) demonstrated that merely tying a rabbit to a board in the supine position produced a fall of body temperature of 1 - 2 degrees Centigrade, followed after a stationary period by a rise of body temperature to 0·5 degrees Centigrade above normal Wright (1942) states that when a man at rest is completely insulated so that he neither loses heat to nor gains heat from the exterior it is found that his body temperature rises by about 2 degrees Centigrade per hour, simply owing to retention of the heat liberated from normal resting metabolism. Since heat production after premedication is at a basal level, these data indicate that a rise of body temperature after premedication must be attributed to insufficient heat loss, while a fall of body temperature during this period is due to excessive heat loss. The following observations indicate the factors acting in each instance.

In India, at a hospital on the plain at an altitude of less than 600 feet, the problem during the hot humid season of the year was to keep cool. Factors promoting heat loss by physical means were encouraged; clothes were reduced to the scantiest proportions and fans were used to promote air movement. In these conditions, although the nervous mechanism of heat loss was relatively depressed by premedication, it was observed that the body temperature rose after premedication in only 27 per cent of cases, it fell in 17 per cent., and no change was observed in 55 per cent. of cases. The maintenance of a normal body temperature in more than half and a rise of body temperature in only 27 per cent. of subjects indicate the success of the positive measures adopted to ensure that heat loss by physical means was adequate. These results are in contrast to the high incidence of heat stroke in alcoholics in this environment. These stuporosed subjects often failed to remove their clothes and/or to turn on their fan before falling asleep. This failure to take the elementary measures necessary to promote maximal heat loss by physical means,

combined with the relative depression of the nervous mechanism of heat loss produced by alcoholic sleep, caused hyperpyrexia, which stimulates metabolism and in turn heat production. Thus, insufficient physical heat loss during the alcoholic depression of the nervous system initiates a vicious circle which results in the complete breakdown of the heat regulation of the body, and heat stroke occurs.

In contrast, at a hospital in a hill station at an altitude of 6,000 feet, the need for protection against physical heat loss after premedication was clearly recognised. In this relatively cold, dry atmosphere, clothing and bedclothes were apt to be heavy rather than light. As the consequence of insulation against physical heat loss, it was found that the mouth temperature after adequate premedication rose in 79 per cent. of cases, and this can be attributed to insufficient heat loss by physical means combined with a failure of the nervous mechanism of heat loss to respond to a rise of body temperature of the order of 1 degree Centigrade. No change was observed in 6 per cent. of cases and the temperature fell in 14 per cent. of cases. Hence the body temperature fell after premedication in 17 per cent. of cases in the hot environment and in 14 per cent. of cases in the cold environment. Thus, after premedication in about one-eighth of the cases of this series, either protection against heat loss by physical means was inadequate or the nervous mechanism of heat loss was still active but was incoordinate and inefficient at the degree of hypnosis produced. But in the cold environment, the protection afforded made excessive heat loss by physical means an improbability, and excessive heat loss in the hot environment was a virtual impossibility. When these conditions are coupled with the resting metabolic rate of the subject, the approximately equal incidence of fall of body temperature after premedication in these contrasting environments indicates a common cause of excessive heat loss, and suggests that overaction by the incoordinate nervous mechanism of heat loss was the relevant factor.

During the degree of hypnosis produced by anæsthetic premedication, it can be concluded that heat production is reduced to a basal level, that the nervous control of heat loss integrated at the cortical level is relatively depressed, and that the physical mechanism of heat loss assumes a dominant rôle in the regulation

of body temperature. The efficiency of the nursing during this period is shown by the fact that a normal body temperature was maintained in 45 per cent. of the subjects of this series. In the remaining cases, the body temperature varied ± 1 degree Centigrade. In 43 per cent. of cases the temperature rose above normal, and this can be attributed to insufficient heat loss by physical means together with an inability of the nervous mechanism of heat loss to react to a rise of body temperature of the order of + 1 degree Centigrade. In 12 per cent. of the cases of this series, the body temperature fell below normal after premedication, and this has been interpreted as an overaction by the relatively depressed nervous mechanism of heat loss; but in conditions of inefficient nursing (which did not occur in this series) it could be attributed to excessive heat loss by physical means.

The behaviour of subjects during basal anæsthesia with avertin or the barbiturates is similar in every respect to that of hypnosis produced with the premedicants quoted above.

In Man, the body temperature during blood-borne anæsthesia rises by 0 5 - 1·5 degrees Centigrade above normal. As anæsthetic induction proceeds, the complete depression of the cerebral cortex is rapidly followed by the anæsthetic depression of the sympathetic and in turn of the para-sympathetic entities of the hypothalamus; with the onset of deep anæsthetic sleep, heat regulation is integrated at the medullary level. A mid-brain preparation, with its hypothalamus cut off, is poikilothermic in its behaviour, but, when blood-borne anæsthesia in Man is carried to the level of deep anæsthetic sleep falling short of medullary depression, the following conditions obtain:

Heat production is at a basal level or less; the cortical and hypothalamic centres of heat regulation are depressed and the regulation of body temperature falls principally upon the physical mechanism of heat loss. But the nervous mechanism of heat loss integrated at a medullary level also plays a part in the regulation of body temperature, for in the absence of other factors, the body temperature at this level of anæsthesia is maintained at from 0 5 - 1·5 degrees Centigrade above normal; moreover when the body temperature rises excessively during this depth of anæsthesia, sweating may occur. These effects indicate that a measure of nervous control of heat regulation is retained during

surgical anæsthesia. Below is a rectal temperature curve taken with a thermocouple in normal theatre conditions. It shows that Man is not completely poikilothermic during surgical anæsthesia, that body temperature is maintained at a higher level than normal during surgical anæsthesia, and that the nervous control of body temperature is sluggish during surgical anæsthesia relative to normal conditions of life.

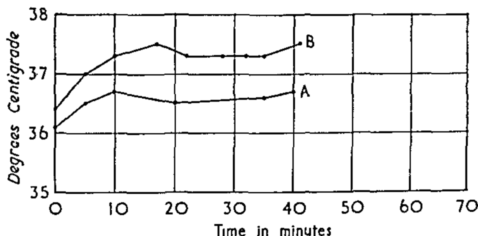


FIGURE 18

Rectal temperature curves during anæsthesia.

Curve A in Figure 18 illustrates the rectal temperature during the removal of an external cartilage of the knee under nitrous oxide, oxygen and di-ethyl ether anæsthesia. During induction, which was swift and trouble-free, the rectal temperature rose from 36·1 to 36 7 degrees Centigrade. It fell by 0 2 degrees Centigrade after the small skin incision was made and then recovered to 36·6 degrees Centigrade as the heat loss from this site was compensated for The body temperature rose to 36 7 degrees Centigrade when the incision was closed at the end of the operation.

Curve B in Figure 18 is the temperature curve of an inguinal hernia performed under the same anæsthetic in the same operating theatre on the same day. In this case the rectal temperature rose from 36 4 degrees Centigrade to 37 3 degrees Centigrade during a troublesome induction and it continued to rise in spite of the additional heat loss produced by the skin incision, for it was 37·5 degrees Centigrade after 17 minutes' anæsthesia. This can be

interpreted as the slow physical dissipation of the excessive heat produced by emotional and physical stress during induction. At 22 minutes the temperature had fallen to 37·3 degrees Centigrade. and it remained at this level until the surgeon commenced to sew up. By the time the skin incision was closed, the body temperature had risen—owing to the elimination of this source of heat loss—to 37 5 degrees Centigrade. These effects indicate that the

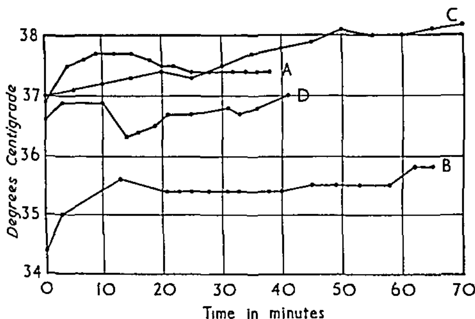


FIGURE 19.

Temperature curves during anæsthesia.

body temperature is maintained at about 1 degree Centigrade above its pre-anæsthetic level during blood-borne anæsthesia, and that nervous control is present though sluggish in its response.

The same effects are observed in Figure 19, where curve A represents the temperature curve of a subject during nephrectomy under avertin, nitrous oxide, oxygen and di-ethyl ether, and curve B that of a mastectomy under nitrous oxide, oxygen and di-ethyl ether. In each instance the body temperature rose during induction, and was stable during anæsthetic maintenance. In curve B—the mastectomy—when the large area of physical heat loss was eliminated by the closing of the skin incision at 58 minutes, heat loss was curtailed; and, because of the inability to adjust

rapidly to changing thermal conditions, the temperature rose by 0·3 degrees Centigrade. Occasional factors such as a high metabolic rate or excessive heat loss produced for example by bleeding modifies the temperature curve during anæsthesia. Curve C represents the temperature curve during a thyroidectomy with avertin, nitrous oxide, oxygen and di-ethyl ether. This was a toxic thyroid with a raised metabolic rate; because heat production was high in this case, except for a slight transient fall of temperature produced by bleeding at 20 minutes, the temperature rose steadily throughout from 37 degrees Centigrade to 38·2 degrees Centigrade. In India, operating in bamboo huts, in still air without fans, with the wet bulb at 85 and more and an air temperature of 100 degrees Fahrenheit and over, heat loss by physical means was practically impossible, and the body temperature during nitrous oxide oxygen and di-ethyl ether anæsthesia often rose to 103 degrees Fahrenheit (39·4 degrees Centigrade). The body temperature could be kept within normal limits by covering the lower extremities with wet towels and directing an air current from a fan from the X-ray plant on to these wet towels. Thus, when physical heat loss is impossible during anæsthesia, the nervous mechanism of heat loss proves inadequate; but heat loss produced by the assisted evaporation of water on the skin surface maintained body temperature within normal limits. At these high body temperatures heat stroke occasionally occurred during anæsthesia, but it is significant that the so-called " ether convulsions " did not occur. Curve D in Figure 19 represents the temperature curve during a tonsillectomy which bled profusely at 10 minutes. The bleeding was followed by a fall of body temperature of 0·5 degrees Centigrade, but when bleeding had been controlled the temperature rose steadily.

Figure 20 illustrates the temperature curves during cystoscopic examination. In curve A, avertin, nitrous oxide, oxygen and di-ethyl ether were used, and the temperature curve shows a rise of body temperature of 0 2 degrees Centigrade In curve B anæsthesia was induced and maintained with chloroform, and it is seen that the body temperature fell to 0 4 degrees Centigrade below the pre-anæsthetic level and was maintained at this low level throughout. One might attribute this fall of body temperature to the depression of the cardiovascular system which is known to

occur during chloroform anæsthesia. Figure 20 also illustrates temperature curves during cholecystectomy. In curve C nitrous oxide, oxygen and di-ethyl ether were used, and it is observed that the body temperature rose progressively throughout and increased slightly when at length the peritoneum was closed. A bilateral

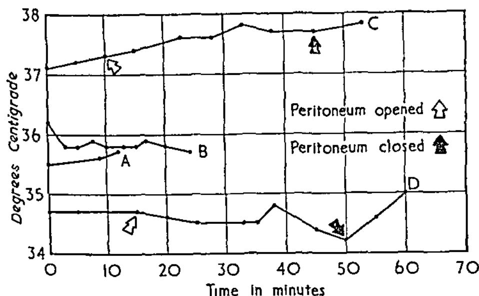


FIGURE 20

Temperature curves during anæsthesia.

sensory and right-sided motor spinal anæsthesia to the level of dorsal 3 with 18 c c. of 1 - 1000 nupercaine and fairly heavy premedication with scopolamine and omnopon were used in the second case illustrated in curve D. About fifteen minutes after the intrathecal injection of the local anæsthetic the rectal temperature was 34·7 degrees Centigrade, this was thought to be due to the low metabolic rate combined with the diminution of the control of heat loss produced by the paralysis of vasoconstrictors. The temperature fell by 0·2 degrees Centigrade when the peritoneum was opened and this fall was again increased at 40 minutes by bleeding. With the rise of blood pressure and the diminished heat loss which followed the closure of the peritoneum at 50 minutes, the body temperature rapidly rose to 35 degrees Centigrade

rapidly to changing thermal conditions, the temperature rose by 0·3 degrees Centigrade. Occasional factors such as a high metabolic rate or excessive heat loss produced for example by bleeding modifies the temperature curve during anæsthesia. Curve C represents the temperature curve during a thyroidectomy with avertin, nitrous oxide, oxygen and di-ethyl ether. This was a toxic thyroid with a raised metabolic rate; because heat production was high in this case, except for a slight transient fall of temperature produced by bleeding at 20 minutes, the temperature rose steadily throughout from 37 degrees Centigrade to 38·2 degrees Centigrade. In India, operating in bamboo huts, in still air without fans, with the wet bulb at 85 and more and an air temperature of 100 degrees Fahrenheit and over, heat loss by physical means was practically impossible, and the body temperature during nitrous oxide oxygen and di-ethyl ether anæsthesia often rose to 103 degrees Fahrenheit (39 4 degrees Centigrade). The body temperature could be kept within normal limits by covering the lower extremities with wet towels and directing an air current from a fan from the X-ray plant on to these wet towels. Thus, when physical heat loss is impossible during anæsthesia, the nervous mechanism of heat loss proves inadequate; but heat loss produced by the assisted evaporation of water on the skin surface maintained body temperature within normal limits. At these high body temperatures heat stroke occasionally occurred during anæsthesia, but it is significant that the so-called " ether convulsions " did not occur. Curve D in Figure 19 represents the temperature curve during a tonsillectomy which bled profusely at 10 minutes. The bleeding was followed by a fall of body temperature of 0 5 degrees Centigrade, but when bleeding had been controlled the temperature rose steadily.

Figure 20 illustrates the temperature curves during cystoscopic examination. In curve A, avertin, nitrous oxide, oxygen and di-ethyl ether were used, and the temperature curve shows a rise of body temperature of 0 2 degrees Centigrade. In curve B anæsthesia was induced and maintained with chloroform, and it is seen that the body temperature fell to 0 4 degrees Centigrade below the pre-anæsthetic level and was maintained at this low level throughout One might attribute this fall of body temperature to the depression of the cardiovascular system which is known to

clinical anæsthetic practice. Although chloroform and trichlorethylene mixtures do not explode, they may decompose in the presence of a naked flame with the formation of a very poisonous gas, phosgene.

The risk of an explosion during clinical anæsthetic practice arises when an explosive mixture comes into contact with a source of ignition. For an anæsthetic mixture to be explosive, its composition must lie between well-defined lower and upper limits. The limits of inflammability vary slightly for a particular anæsthetic as the propagation of the flame is upwards, horizontal or downwards and the range diminished in this order. Table 64 constructed from values quoted by Rayner (1938), shows the heat of combustion and the limits of inflammability of the anæsthetics in common clinical use. The ethers and cyclopropane are seen to be the most powerful explosives. When mixed with air, the limits of inflammability of the anæsthetics in common clinical use lie between about 1·7 per cent. and 36 per cent. but when mixed with oxygen, the range is extended and lies between 1·8 per cent. and 85 per cent. For a particular mixture, complete safety from explosion is achieved only when a figure is adopted below the lower limit of inflammability for upward propagation. Thus, the lower limit of inflammability for methane in air is 4·5 per cent. but in mining practice, an atmosphere which contains 3 per cent. of methane is regarded as dangerous. Hence, if the figures in Table 64 are accepted, complete safety is achieved with the ethers at some concentrations below 1·7 per cent. with cyclopropane and ethylene below about 2·4 per cent. and with ethyl chloride at some concentration in the mixture below 4 per cent.

The investigations of Townend and his colleagues, however, show that this is not the whole story. Townend and Chamberlain (1936, 1937) studied the explosive characteristics of mixtures of the lower paraffins and di-ethyl ether with air, and in each case two ignition points were observed, a lower and a higher. Only di-ethyl ether will be cited in this discussion, but its behaviour is typical of the other hydrocarbons and in turn of the inflammable anæsthetics in common clinical use. The lower ignition point of di-ethyl ether - air mixture at atmospheric pressure was found to be about 180 degrees Centigrade and at this temperature the

The evidence discussed indicates that Man is not completely poikilothermic during anæsthesia but that the delicate nervous control of body temperature is diminished. Heat production is reduced to a basal level: a greater deviation of body temperature from normal limits is required to activate the nervous mechanism of heat loss, and the response of the medullary and spinal centres to thermal effects are sluggish. In the absence of occasional factors, the body temperature rises above normal during blood-borne anæsthesia. The only observation made during chloroform anæsthesia suggests there may be a fall of body temperature when this anæsthetic is used. This coincides with the views of earlier observers who had extensive experience with chloroform, but Davis (1909) states that a fall of temperature of equal intensity occurs with both di-ethyl ether and chloroform. During spinal anæsthesia of sufficient height, a fall of body temperature can be anticipated. In the conditions obtaining in modern surgical practice, these alterations of body temperature seldom exceed $\pm 1 \cdot 5$ degrees Centigrade of normal, and variations of this order are seldom if ever detrimental to the subject. It must be remembered that during anæsthesia the regulation of the physical mechanism of heat loss is the only effective method available to the anæsthetist for the control of the body temperature of the subject. During conditions of increased metabolism or of excessive heat retention, heat loss can be increased by light clothing or the lack of it, by adequate air movement and by the evaporation of water on the skin surface. When heat loss is, on the contrary, excessive, heavy clothing, heating of the environment or even the direct application of heat to the subject must be combined with intravenous fluids and oxygen to maintain the body temperature to within $\pm 1 \cdot 5$ degrees Centigrade of normal.

Anæsthetic Explosions. In a survey of anæsthetic explosions in America, Woodbridge (1937) estimates that the incidence of explosions when di-ethyl ether, ethylene and cyclopropane are used in clinical practice is 2 - 4 per 100,000 anæsthetics, and the mortality about 1 in every 43 anæsthetic explosions.

All the volatile anæsthetics in common clinical use, except chloroform, trichlorethylene and nitrous oxide, form explosive mixtures with air or oxygen in the conditions which obtain in

The higher ignition point for di-ethyl ether - air mixtures at atmospheric pressure lies between 430 degrees Centigrade and about 600 degrees Centigrade. At this temperature a violent

IGNITION OF ETHER—AIR MIXTURES

TEMPERATURE & PRESSURE LIMITS FOR COOL FLAMES WITH 5% MIXTURE.

10% ETHER
5 " "
2 " "
1 " "

TEMPERATURE °C

PRESSURE ATMOSPHERES

FIGURE 21

Ignition of ether - air mixtures

explosion is produced in which combustion proceeds to completion, with the formation of carbon dioxide and water.



$$(C_2H_5)_2O + 6\ O_2 \longrightarrow 4\ CO_2 + 5\ H_2O$$

Thus, two distinct ignition systems were observed for mixtures of di-ethyl ether in air; one for the normal hot flame propagation which produces a violent explosion and one for the innocuous cool

mixture does not explode but burns with the 'cool flame' discovered by Perkins in 1882. In a light room the cool flame is hardly visible; in the dark its colour is seen to be pale blue. Propagation is slow, and it travels at a velocity of about one metre in five seconds. Its maximum temperature never exceeds about 270 degrees Centigrade and it is not in itself dangerous. On the basis of Le Chatalier's *thermal view of flame propagation, the cool*

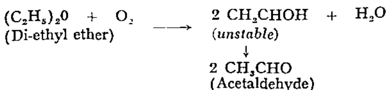
TABLE 64.

VOLUMETRIC LIMITS OF THE INFLAMMABILITY OF ANÆSTHETIC MIXTURES

(AFTER RAYNER [1938])

Anæsthetic	Heat of Combustion (cal. per gm mol.)	Limits with air (%)	Limits with oxygen (%)
Di-ethyl ether	660	1·8 - 36	2·1 - 82
Di-vinyl ether	—	1·7 - 27	1 85 - 85
Cyclopropane	530	2·4 - 10	2·4 - 50
Ethylene	330	2 7 - 28	2 9 - 80
Ethyl chloride	330	4·0 - 15	
Hydrogen	58	4 0 - 70	
Chloroform	110	Non-explosive	
Trichlorethylene	—		
Nitrous oxide	(— 19)		

flame is assumed to develop just enough heat to raise the unburnt mixture to its lower ignition point, and combustion is limited to an oxidation stage in which acetaldehyde is the principal end-product.

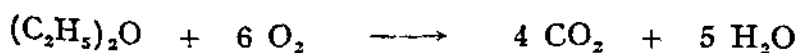


The higher ignition point for di-ethyl ether - air mixtures at atmospheric pressure lies between 430 degrees Centigrade and about 600 degrees Centigrade. At this temperature a violent

FIGURE 21

Ignition of ether - air mixtures

explosion is produced in which combustion proceeds to completion, with the formation of carbon dioxide and water.



$$(C_2H_5)_2O \quad + \quad 6\ O_2 \quad \longrightarrow \quad 4\ CO_2 \quad + \quad 5\ H_2O$$

Thus, two distinct ignition systems were observed for mixtures of di-ethyl ether in air; one for the normal hot flame propagation which produces a violent explosion and one for the innocuous cool

flame in which the mixture burns relatively slowly. Figure 21, taken from the work of Townend and Chamberlain (1937), shows that at a pressure of one atmosphere hot flame propagation occurs

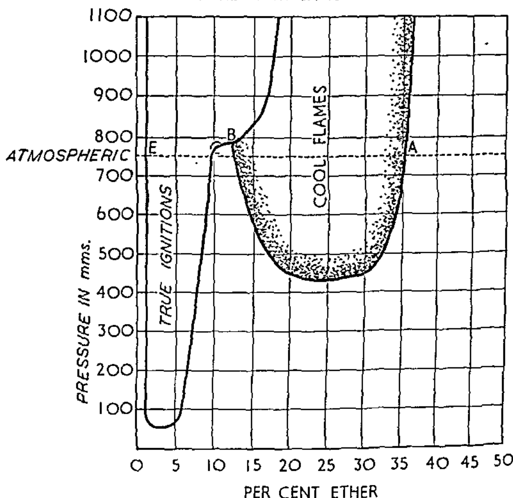


FIGURE 22

Limits of ignitability of ether - air mixtures at 20 degrees Centigrade (Horizontal propagation tube 5 cm. diameter.)

in a given di-ethyl ether - air mixture at and above its upper ignition temperature which is seen to be 430 degrees Centigrade for a 10 per cent mixture; 450 degrees Centigrade for a 5 per cent.;

540 degrees Centigrade for a 2 per cent. and 610 degrees Centigrade for a 1 per cent. mixture of di-ethyl ether in air. It shows too, that these mixtures do not explode but burn with a cool flame between the range of 180 degrees Centigrade and 270 degrees Centigrade (A - B). They are not inflammable between 0 degrees Centigrade and 180 degrees Centigrade (D - A) and at a pressure of one atmosphere, these observers also found that they are not inflammable between a temperature of 270 degrees Centigrade and the upper ignition temperature of the particular mixture. Thus, a 10 per cent. mixture of di-ethyl ether in air is not inflammable between the range of 270 degrees Centigrade and 430 degrees Centigrade (B - C).

Figure 22 (after Townend*) shows the limits of ignition of di-ethyl ether-air mixtures at room temperature and the lettering, A, B, C and E, of the four mixture composition limits shown in this figure correspond with the ignition temperature limits shown in Figure 21. At atmospheric pressure, it is seen that di-ethyl ether - air mixtures below about 1·5 per cent., are not inflammable; mixtures between 1·5 per cent. and about 9 per cent. (E - C) propagate a true explosion; between 9 per cent. and about 13 per cent. (C - B) di-ethyl ether-air mixtures are not inflammable; and mixtures of di-ethyl ether in air of 13 per cent. to about 35 per cent. (B - A) burn with a cool flame.

In modern anæsthetic practice, however, di-ethyl ether - oxygen mixtures are almost invariably used and because of the absence of the damping effect of nitrogen, the range of hot flame propagation is increased.

During clinical anæsthesia, inflammable mixtures are to be found in the anæsthetic machine itself and in the theatre atmosphere.

The partial pressure of di-ethyl ether in the ether container of an anæsthetic machine depends upon the temperature of the liquid di-ethyl ether in this vessel. This anæsthetic mixture leaving this container to enter alveolar air, *via* the anæsthetic reservoir, the breathing tube and the mask of the machine, has a di-ethyl ether content of about 6 per cent. during anæsthetic maintenance. Such a mixture is capable of propagating a hot flame; but even if the concentration of di-ethyl ether exceeds the upper limit of hot flame

* Personal communication

flame in which the mixture burns relatively slowly. Figure 21, taken from the work of Townend and Chamberlain (1937), shows that at a pressure of one atmosphere hot flame propagation occurs

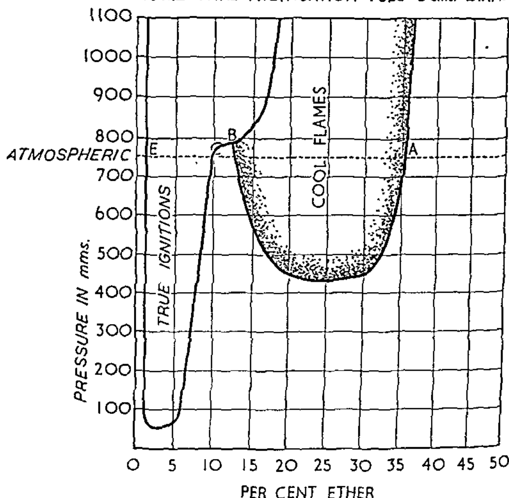


FIGURE 22.

Limits of ignitability of ether - air mixtures at 20 degrees Centigrade (Horizontal propagation tube 5 cm diameter)

in a given di-ethyl ether - air mixture at and above its upper ignition temperature which is seen to be 430 degrees Centigrade for a 10 per cent. mixture; 450 degrees Centigrade for a 5 per cent.;

breathing is employed, the anæsthetic mixture escapes into the theatre atmosphere and a di-ethyl ether - air mixture is produced which may explode or burn with a cool flame.

Horton (1941) states that there is no risk of an explosion if the leak from a closed system is relatively small and is separated from the source of ignition by more than 12 inches. If the bronchial fistula is small, or if the escape of the anæsthetic mixture is reduced to minimal proportions by a suitable dressing, it can be assumed that a source of ignition more than 12 inches distant from the fistula involves little explosive risk.

In a typical operating theatre of 4,488 cubic feet capacity, with three doors, a serving hatch and forced heating and ventilation, an average of about 2½ lbs. of di-ethyl ether is used in a semi-closed system of breathing by anæsthetic clerks during an operation session lasting for 3½ hours. If 2½ lbs. of di-ethyl ether escaped into a sealed room of this capacity and assumed a state of gaseous equilibrium throughout this space, a 0.27 per cent. mixture of di-ethyl ether in air would be produced. Reference to Figure 22 shows that a 0.27 per cent. mixture of di-ethyl ether in air neither explodes nor burns with a cool flame. In clinical anæsthetic practice, however, the escape of this amount of di-ethyl ether from the expiratory valve of the anæsthetic machine is spread over about 3½ hours; moreover this theatre atmosphere is replaced fifteen to twenty times per hour by forced ventilation, and other means of air movement tend to reduce its concentration still further. The entrance of steam into this operating theatre also reduces the possibility of explosion, for, to the damping effect of water vapour on flame propagation must be added the inhibition of electrostatic sparks because of the increased electrical conductivity of a water-laden atmosphere. At first sight these conditions tend to engender a complacency that is not justified, for foci of high concentrations of di-ethyl ether in this theatre atmosphere may readily produce high spots of explosive mixture.

The most obvious high spot of explosive mixture is to be found under the towels which drape the subject's head Di-ethyl ether is two and a half times heavier than air and passes from this site to the floor under the head of the operating table. Thence it flows in a steady stream at floor level to the outlet vent in the theatre floor A high spot of explosive mixture may occur anywhere in

propagation, it must in the interests of safety be assumed that a true explosion will occur in the anæsthetic machine in the presence of a source of ignition.

It is suggested that water vapour, carbon dioxide, nitrogen or added helium by their damping effect on the anæsthetic mixture give a measure of protection against explosion. These substances lower the range of inflammability of explosive mixtures in keeping with their molecular heat capacity and their thermal conductivity. Carbon dioxide, which has a higher molecular heat capacity than either nitrogen or helium, is most effective in this respect. Nitrogen has a higher molecular heat capacity than helium, but the thermal conductivity of helium is about six times that of nitrogen and equal volumes of nitrogen and helium have about the same damping effect. Water vapour is the least effective damping agent.

Since the flow of anæsthetic gases is now regulated with dry flowmeters and because, in a semi-closed system of breathing, nitrogen is excreted throughout anæsthesia, only the effect of the carbon dioxide and water vapour accumulated as a result of rebreathing need be considered when a semi-closed system is used. Guedel (1937) states that carbon dioxide in respirable quantities has no discernible effect upon the inflammability of explosive anæsthetic mixtures, and he asserts that the humidity produced by complete rebreathing for about twelve unit respiratory efforts, is sufficient to prevent static sparks in the anæsthetic machine itself.

In a closed system of breathing, carbon dioxide and water vapour are present in the expiratory phase and the inspiratory phase is free of these substances; in a closed system of breathing nitrogen can be retained throughout anæsthesia. Hence, it can be assumed that static sparks may be prevented in the expiratory phase, while the nitrogen content of the inspiratory phase can be expected to reduce the range of flame propagation to about that of di-ethyl ether - air mixtures. If a closed system of breathing is in fact free from leaks, explosive anæsthetic mixture cannot escape into the theatre atmosphere In the absence of a major source of ignition in the machine itself, an efficient closed system of breathing provides complete protection from anæsthetic explosions.

When a closed system of breathing leaks or when a bronchial fistula is present and when an open or semi-closed system of

cannot occur if the diathermy is used in the orthodox manner, in short bursts, and its accumulation in significant amounts is prevented if the irrigating liquid is frequently replenished. High spots of explosive mixture which might occur from the diffusion of inflammable anæsthetics from circulating blood are dangerous only if they occur in sites contiguous with the pulmonary system or else in an enclosed space.

All the other inflammable anæsthetics in common clinical use, except ethylene, are heavier than air; when they escape into the theatre atmosphere they behave in a manner which is identical with that of di-ethyl ether. The density of ethylene is 1·19 while that of air is 1·20: when ethylene escapes into the theatre atmosphere, by diffusion and mass movement, it rapidly tends to assume a state of gaseous equilibrium throughout the whole theatre atmosphere. It is unlikely therefore that ethylene will form high spots of explosive mixture. This was confirmed by Cheney and Folkman (1930), who determined the ethylene content of the operating theatres of a number of hospitals, taking as many as 290 separate readings in various parts of a single operating theatre. When a semi-closed system of breathing was used, the ethylene content of the theatre atmosphere was found to be below the lower limit of inflammability of an ethylene-air mixture, except at one spot—namely, in the area within 6 inches of the expiratory valve in the line of the vent: there it was 3 6 per cent., while at a distance of 12 inches its concentration was only 2 36 per cent. If forced ventilation is employed, ethylene is extracted at approximately the same rate as air which in the case of the operating theatre described above is about 89,000 cubic feet per hour. In modern anæsthetic practice, however, ethylene is invariably used in a closed system of breathing, if this is an efficient system, the possibility of its presence in the theatre atmosphere does not arise.

High spots of explosive mixture do not ignite spontaneously. Possible sources of ignition during surgical procedures are discussed below.

When a conductor of electricity is supported on a non-conductor, e.g. a theatre trolley with rubber-tyred wheels, any electricity produced on the conductor by friction accumulates until at length the conductor is charged with static electricity. If any part of this charged but insulated conductor is touched by another

the line of this current from the expiratory valve to the outlet vent. Moreover, in the course of this current, di-ethyl ether may be deviated into *cul de sacs* of ill-ventilation or patches of dead space, whose location depends upon the configuration of the particular theatre; in such patches of dead space, di-ethyl ether may accumulate and ultimately reach an explosive mixture. In the operating theatre of a teaching hospital, the air currents produced by the movements of the usual—and relatively large—number of surgical ward clerks make such accumulation improbable if not impossible. In quiet operating theatres, on the contrary, where only essential staff are present during surgical procedures, the accumulation of di-ethyl ether in patches of dead space is possible; moreover, there may be stratification of di-ethyl ether in the theatre atmosphere. If stratification occurs, the most explosive mixtures of di-ethyl ether—the weak ones—will be found in the upper reaches, while cool-flame mixtures—the concentrated ones—occur in the lower levels of the theatre atmosphere; a real danger exists from the fact that a cool flame may travel over a considerable distance and give rise to a hot flame should it pass into an explosive mixture. Thus a cool flame initiated at some distance from the anæsthetic machine can travel back to the machine and give rise to a violent explosion

Finally, inflammable anæsthetics diffuse from circulating blood into tissue spaces such as the peritoneum, the pleura, the bladder, etc , where high spots of explosive mixture may occur. Horton (1941) states that when inflammable anæsthetics are employed, diathermy should not be used on lung tissue, in the pleural cavity and when a bronchial fistula is present; to these conditions may be added lumbar sympathectomy, during which surgical procedure the pleura may be inadvertently opened. Guedel (1937) describes the rupture of the urinary bladder during ethylene anæsthesia while the surgeon was performing a cystoscopic fulguration of a bladder papilloma. This accident may have been due to the explosion of ethylene which had diffused from the bladder capillaries into a large air bubble above the irrigating liquid in the bladder, but it may also have been caused by the explosion of hydrogen liberated by the too-prolonged passage of the diathermy current through the water present in the bladder. The liberation of hydrogen in significant amounts in the bladder

cannot occur if the diathermy is used in the orthodox manner, in short bursts, and its accumulation in significant amounts is prevented if the irrigating liquid is frequently replenished. High spots of explosive mixture which might occur from the diffusion of inflammable anæsthetics from circulating blood are dangerous only if they occur in sites contiguous with the pulmonary system or else in an enclosed space.

All the other inflammable anæsthetics in common clinical use, except ethylene, are heavier than air; when they escape into the theatre atmosphere they behave in a manner which is identical with that of di-ethyl ether. The density of ethylene is 1·19 while that of air is 1·20: when ethylene escapes into the theatre atmosphere, by diffusion and mass movement, it rapidly tends to assume a state of gaseous equilibrium throughout the whole theatre atmosphere. It is unlikely therefore that ethylene will form high spots of explosive mixture. This was confirmed by Cheney and Folkman (1930), who determined the ethylene content of the operating theatres of a number of hospitals, taking as many as 290 separate readings in various parts of a single operating theatre When a semi-closed system of breathing was used, the ethylene content of the theatre atmosphere was found to be below the lower limit of inflammability of an ethylene-air mixture, except at one spot—namely, in the area within 6 inches of the expiratory valve in the line of the vent: there it was 3 6 per cent., while at a distance of 12 inches its concentration was only 2 36 per cent. If forced ventilation is employed, ethylene is extracted at approximately the same rate as air which in the case of the operating theatre described above is about 89,000 cubic feet per hour In modern anæsthetic practice, however, ethylene is invariably used in a closed system of breathing; if this is an efficient system, the possibility of its presence in the theatre atmosphere does not arise

High spots of explosive mixture do not ignite spontaneously. Possible sources of ignition during surgical procedures are discussed below.

When a conductor of electricity is supported on a non-conductor, e.g. a theatre trolley with rubber-tyred wheels, any electricity produced on the conductor by friction accumulates until at length the conductor is charged with static electricity. If any part of this charged but insulated conductor is touched by another

conductor, the whole of its charge is at once lost. If a charged conductor is brought sufficiently near to a body of opposite potential then, in an effort to equalize the electrical potential, it discharges across the gap with the production of a spark. Friction between wool, silk, rayon etc. and other non-conductors favours the accumulation of very high electric charges on almost every article of theatre furniture. This is especially so in a dry atmosphere and when the theatre atmosphere is air-conditioned, for dry air is a bad conductor of electricity. On the other hand when the theatre atmosphere is humid, the high water vapour content of air increases its electrical conductivity, static electricity fails to accumulate in significant amounts, and electrostatic sparks are unlikely. Rovenstine (1936) states that there is no risk of electrostatic sparks if the relative humidity of the theatre atmosphere exceeds 54 per cent. but Adriani (1946) reports that anæsthetic explosions initiated by electrostatic sparks have occurred when the humidity was as high as 65 per cent. If the theatre furniture is efficiently earthed, however, static electricity cannot accumulate and such sparks cannot occur. Efficient earthing is achieved by means of a metal chain attached to the conductor and making contact with the theatre floor. Unless sparks are to occur at its point of contact with the floor, the drag-chain must be of bronze and free from oil, grease or lacquer, and the floor itself must be a good conductor. Modern operating theatres have granolithic floors which have proved to be good conductors; but drag-chains become useless when the floor is covered with rubber, cork, linoleum, carpet, or some other non-conductor. In a dry atmosphere, the risk of the ignition of explosive mixtures by an electrostatic spark is very real; and in America, where many anæsthetic explosions have been reported from this cause, elaborate systems have been devised to ensure that the anæsthetic apparatus, the anæsthetist, the patient and operating table are always earthed. The incidence of anæsthetic explosions caused by an electrostatic spark is low in Great Britain, but Ironside (1935) and Chivers (1943) have each reported an anæsthetic explosion in which the source of ignition was a static spark. In the air-conditioned theatre in which Ironside's explosion occurred the friction of a pillow on the rubber top of an un-earthed theatre trolley produced a high static charge, for when a finger was placed on the metal upright of the trolley,

a spark was produced which was felt and seen in broad daylight. Except in air-conditioned theatres, static electricity as a source of ignition tends to be under-rated in this country. This view is not justified. Thus, at Guy's Hospital in a theatre which is not air-conditioned, Professor G. Stead (1945) observed that the friction of a pillow on the canvas top of a theatre trolley produced a sufficient charge to light a spirit lamp or a piece of cotton wool soaked in di-ethyl ether. Evidently, even in the moist atmosphere of the British Isles, the theatre floor must be a good conductor of electricity, and efficient drag-chains fitted and used.

Since the anæsthetic machine is the source of explosive mixtures, anæsthetists in dry climates have been exercised as to the possibility of the accumulation of significant electrical charges in or on the machine itself.

The passage of dry anæsthetic gases through dry flowmeters and rubber tubes and the movement of taps and valves produce sufficient friction in the machine to generate an electric charge but it is doubtful whether it can accumulate in significant amounts. However, this possibility is sufficiently real to make the use of conducting rubber a substantial contribution to safety. On the other hand, the water vapour of expired air reduces the possibility of the accumulation of static charges while rebreathing increases the carbon dioxide and water vapour content of the anæsthetic mixture and reduces the range of its inflammability. Moreover, Townend's observations raise the possibility that anæsthetic mixtures in the machine may be incapable of propagating either a hot or a cool flame. On balance, it is improbable that the ignition responsible for anæsthetic explosions ever originates in the anæsthetic machine itself.

In a dry atmosphere, friction on the outside surface of the anæsthetic machine generates an electrical charge. The rubbing of the rubber anæsthetic reservoir or breathing tubes on outside objects during the phases of respiration may also generate static charges in an un-earthed machine. It must be remembered too, that the friction produced when a mask is applied or removed may be followed by an electrostatic spark in a dry atmosphere; Guedel (1937) believed that this source of ignition was responsible for many of the anæsthetic explosions that he discussed. Coating the face of the subject with vaseline before the facepiece is applied

will materially reduce the possibility of a static spark at this site. Adriani (1946) is of the opinion that anæsthetic machines as normally used are not responsible for the generation of static discharges which may cause anæsthetic mixtures to explode. In a closed system of breathing, the possibility of an internal explosion is remote if nitrogen is retained throughout anæsthesia; this possibility is further reduced in a machine with the anæsthetic reservoir in the inspiratory phase, when the humidity of the inspiratory phase is increased by sufficient rebreathing and when non-hydroscopic soda lime is used or water is placed in the anæsthetic reservoir. Since in addition, anæsthetic mixtures cannot escape into the theatre atmosphere from an airtight closed system, it can be concluded that absolute protection from anæsthetic explosions is achieved by the use of an efficient closed system of breathing. Similarly, internal explosions produced by static discharges are improbable in semi-closed systems of breathing, but when an open or a semi-closed system of breathing is employed, the anæsthetic mixture escapes into the theatre atmosphere. High spots of anæsthetic mixture may occur in this atmosphere and may be ignited by an electrostatic spark, but this possibility is eliminated if earthing is efficient throughout the whole operating theatre. But there are sources other than electrostatic sparks which may produce hot or cool flame propagation in these high spots of anæsthetic mixture in the theatre atmosphere and it is now proposed to discuss them.

Surgical instruments such as the cautery and the diathermy, which are designed to burn, cut or coagulate, are obvious sources of ignition. They are legitimate aids to surgery and when they are used, the anæsthetist must ensure that they do not come into contact with high spots of explosive mixture. This can be achieved only if an efficient closed system of breathing is employed or if non-inflammable anæsthetics are used. It should also be remembered that fires have occurred when the diathermy knife has been used before spirit and other inflammable lotions used to cleanse the skin have had time to evaporate. In each instance however the source of ignition occurs about three feet above floor level and is unlikely to encounter high spots of explosive mixture when heavier-than-air inflammable anæsthetics are used; this is particularly so when the Trendelenburg position is adopted.

(Ethylene, with a density about the same as that of air, is not included in the foregoing.) All other forms of naked flame, such as spirit lamps, gas or electric fires etc., should never be permitted in the operating theatre. Another occasional form of naked flame occurs in dental practice when hot air from a syringe whose metal nozzle has been heated in a flame is blown into a tooth cavity, for if the nozzle has been excessively heated, it is possible to ignite an explosive anæsthetic mixture.

The remaining sources of ignition likely to be encountered in the operating theatre are due to defective electrical equipment. Faulty flex, poor connections or short circuits in cystoscopes, bronchoscopes, œsophagoscopes etc. may produce sparks. When excessive voltages are used to light the small lamps of these instruments or any other form of pea lamp used for surgical exploration, the overheated electric bulb may ignite an explosive mixture Protection against the overheating of these small bulbs can be ensured by always using a dry battery whose maximum voltage is not more than 25 per cent. above the rated voltage for the particular lamp. A modern type of gas-exhausted bulb for these instruments provides complete protection, for they cannot overheat. An uncommon explosion recently occurred when a defective cystoscope bulb was soaked in spirit prior to use. Spirit or alcohol vapour leaked into the bulb which exploded when the current was turned on and the filament of the bulb heated. Such occasional and accidental sources of ignition can be avoided only by careful and frequent inspection of equipment.

Other ancillary equipment which is activated by electricity, such as motors used to drive suckers, surgical saws, etc may be defective and cause sparks. Such occasional sources of ignition may be eliminated if switches are of the spark-proof type, if plug-in connections are of the interlocking type, if flexible leads are well-insulated and sound, if switches—particularly foot-switches—are spark-proof, if electric motors are spark-proof and are enclosed and if the spark-gap of diathermy machines are enclosed. X-ray equipment is another possible source of ignition, for although it should be spark-proof, defects may be present; it is clear that only by the constant and careful supervision of these types of apparatus by a skilled technician can this source of ignition be eliminated.

Spontaneous ignition may occur when oxygen comes into contact with oil or grease. The screw-threads of oxygen cylinders and reducing-valves should therefore be kept clean and dry; fibre or lead washers should be used, for leather washers often contain grease. Again, the careless fitting of reducing-valves to cylinders may result in fire, for if dirt enters the seating of a reducing-valve attached to any type of cylinder, the valve may fire or may fail to cut off efficiently and the excessive pressure in the valve may burst the diaphragm and/or its casing with the risk of fire. Separate reducing valves should be used for each anæsthetic gas, for a valve may retain some of the gas previously used; ethylene becomes more explosive when mixed with nitrous oxide, while oxygen increases the range of inflammability of all explosive mixtures. When fitting a reducing-valve to a cylinder, screw threads should be cleansed and the dust must be blown from the cup of the cylinder. With the valve screwed tightly into its seating, and its outlet wide open, the cylinder should then be slowly turned on. If the valve does not chatter, the outlet is closed and the cylinder is then turned on fully. Chattering valves indicate that the pin is not seating efficiently. They are dangerous and should be immediately withdrawn from service.

Since surgical intruments designed to burn or coagulate are in constant surgical use and because accidental sources of ignition often occur, it is clear that the only sure methods of avoiding an anæsthetic explosion are to use an efficient closed system of breathing or to use non-inflammable anæsthetic agents. When a semi-closed system of breathing is employed, the risk of explosion can be minimized or completely eliminated in two ways. Epstein (1944) suggested that di-ethyl ether can be absorbed by passing it through activated charcoal. An alternative method, applicable to all inflammable anæsthetic mixtures, would be to evacuate explosive mixtures direct from the expiratory valve of the anæsthetic machine to the exterior of the theatre. This could be achieved with a suitable cowling situated in the floor under the head of the operating table and connected with the ventilating exhaust fan. In the absence of such a system of forced evacuation, care should be taken to see that all electrical equipment is positioned out of the line of the current from the expiratory valve of the anæsthetic machine to the outlet vent. Finally, there is no

technical reason why all electrical equipment such as suckers, diathermy, etc. should not be positioned at some site outside the operating theatre and the anæsthetic room.

REFERENCES.

Central Nervous System.

1. COOPER, ASHLEY (1836). *Guy's Hosp Rep.* 1, 457.
2. COURVILLE, C. B. (1938). *Ann. Surg.* 107, 371.
3. GILDEA, E. F., and COBB, S. (1930). *Arch. Neurol. and Psychiat.* 23, 876.
4. GOMEZ, L., and PIKE, F. H. (1909) *Jour. exper. Med.* 11, 257.
5. LOWENBURG, K, WAGGONER, R W, and Zhinden, T. (1936). *Anal. Surg.* 104, 901.
6. PAYNE, R. Y. (1936) *Guy's Hosp. Rep* 86, 461
7. WEINGERGER, L. M., GIBBON, M. M, and GIBBON, J. H. (1940). *Arch. Neuro and Psychiat.* 43, 615, 961

Blood, Blood Volume and Spleen.

1. ADOLPH, E. F., and GERBASI, M J. (1933). *Am. Jour Physiol.* 106, 35.
2. BARBOUR, H. G., and BOURNE, W. (1923). *Am Jour Physiol.* 67, 399.
3. BARCROFT, J., and HARRIS, H A., ORCHOVATS, D and WEISS, R. (1925). *Jour. Physiol.* 60, 243.
4. BARCROFT, J., and ROTHSCHILD, P. (1930). *Arch Pharmacodyn. Therapie* 38, 569.
5. BEECHER, H. K. (1940) "The Physiology of Anæsthesia." 2nd Ed p 226.
6. BERT, P. (1878) "La Pression barometrique" Paris
7. BHATIA, B B and BURN, J H. (1933). *Jour. Physiol.* 78, 257.
8. BOYCOTT, A. E., and JONES, C PRICE (1922). *Jour. Path & Bact* 25, 335.
9. BUCKMASTER, G. A., and GARDNER, J A. (1907) *Proc Roy Soc.* sB. 79, 555.
10. BRUGER, M., BOURNE, W., and DREYER, N B. (1930) *Amer Jour. Surg.* 9 82
11. COOK, F. S., and ROSE, M. I. (1930). *Amer. Jour Physiol* 92, 240.
12. DRABKIN, D. L., and EDWARDS, D J. (1936). *Amer. J Physiol.* 177, 328
13. ELLIS, M. M., and BARLOW, O. W. (1924). *Jour Pharm. exper. Therap.* 24, 258.
14. FÜHNER, H., and NEUBAUER, E. (1907). *Arch exper Path. Pharm.* 56, 333.
15. GANGEE, Z. (1896). *Z Biol.* 34, 505
16. GELLHORN, E., and PACKER, H. C (1939) *Proc. Soc exper. Biol & Med.* 41, 345
17. GOLLWITZER-MEIER, K., and KROETZ (1924). *Biochem. Zeit* 154, 82
18. GORDON, W. (1947) Personal communication
19. GREGG, H W., LUTZ, B. R, and SCHNEIDER, E C (1919). *Amer Jour. Physiol* 50, 216, 302
20. HALDANE, J S., KELLAS, A S, and KENNAWAY, E L (1919). *Jour. Biol. Chem.* 43, 3, 15.
21. HAMBURGER, W W, and EWING, F F. (1908) *J A M A.* 51, 1586
22. HENDERSON, Y. (1938) "Adventures in Respiration" Baltimore. p. 57
23. HENDERSON, Y., and GREENBURGER, L. A. (1934). *Amer. Jour. Physiol.* 107, 37.
24. HENDERSON, Y, and HAGGARD, H. W (1920) *Jour Biol. Chem* 43, 3, 15.
25. HURTADO, A. (1932) *Amer Jour Physiol* 100, 487.
26. KILLIAN, H., and MORITY, M. (1931). *Z exper Med.* 79, 173
27. KOFHLER, A. E, BRUNQUIST, E H, and LOEVENHART, A. S (1925). *Jour Biol Chem.* 64, 313
28. LEAKE, C. D (1922) *J.A.M.A* 72, 1687.
29. MANCHOT, W., and BRANDT, W. (1909) *Leibigs Ann* 70, 260

30. Mann, F. C. (1916). *J.A.M.A.* 67, 172.
31. McAllister, F. F. (1938). *Amer. J. Physiol.* 124, 391.
32. McMechan, F. M. (1926). *Brit. med. J.* 2, 1107.
33. Meyer, O. O., Seevers, M. H., and Beatty, S. R. (1935). *Amer. J. Physiol* 113, 167.
34. Peters, J. P, and Van Slyke, D. D. (1923). "Quantitative Clinical Chemistry." Baltimore. p. 967.
35. Rabinovich, M. (1927). *Brit. Jour. exper. Path.* 8, 343.
36. Reeve, E. G. B. (1946). Personal communication.
37. Rothmann, A. (1888). *Vjschr. Zahnheilk.* H2.
38. Sanford, N. H. (1926) *Anest. & Analg.* 5, 216.
39. Schafer, E. A., and Moore, B. (1896). *Jour. Physiol.* 20, 1.
40. Searles, P. W., and Essex, H. E. (1936). *Proc. Staff Meet. Mayo. Clin* 11, 481.
41. Stewart, J. D (1937) Quote from Beecher, H. K., "The Physiology of Anæsthesia." p. 228 1940. Oxford University Press.
42. Straus, D C, and Rubin, H. H. (1927). *J.A.M.A.* 88, 310.
43. Taylor, I. B., and Waters, R. M. (1935). *Anest. & Analg.* 14, 276.
44. Ulbrich (1888). *Vjschr. Zahneilk.* H2.
45. Van Liere, E. J. (1943) "Anoxia." Chicago. p. 43 62.
46. Webster, W. (1929). *Anesth. & Analg* 8, 106.
47. Waters, R. M, and Schmidt, E. R. (1934). *J.A.M.A.* 103, 975.
48. Weiss, S (1926). *Proc. Soc. exper. Biol. Med.* 23, 363.
49. Wright, S. (1942) "Applied Physiology." London. 7th Ed. p. 482.

Respiratory System.

1. Beecher, H. K, and Adams, R (1942) *J.A M A.* 118, 1204.
2. Boycott, A. E., Damant, G. C. C, and Haldane, J. S. (1908). *Jour. Hyg. Camb.* 8, 342.
3. Brewer, N., Luckhardt, A. B., Lees, W. M, and Bryant, D. S. (1934). *Anesth & Analg.* 13, 257
4. Brock, R C (1946). "The Anatomy of the Bronchial Tree." p. 8. Oxford University Press, London.
5. Brunn, H., and Brill, S. (1930) *Ann. Surg.* 92, 801.
6. Carlson, H A (1923) *Jour. Thorac. Surg.* 2, 196.
7. Coryllos, P N., and Birnbaum, G. L. (1928). *Arch Surg Chicago.* 16, 501.
8. Engel, S, and Newns, G H (1941) *Lancet* 1, 212.
9. Foss, H L., and Kupp, J H (1930). *Surg Gyn & Obst.* 51, 789.
10. Graham, E. A (1923) *J.A.M.A* 80, 439.
11. Harris, T A. B, (1942). *Brit. Jour Anæsth.* 18, 11.
12. Johnson, V E (1931) *Am J. Surg.* 11, 478
13. Keith, A (1909) "Further Advances in Physiology." p 184 Edward Arnold, London.
14. King, D. S (1933). *Surg Gynec Obst.* 56, 43.
15. Lumsden, T (1923) *Jour Physiol* 57, 153, 354
16. Marshall, G. (1923). "Official History of the War." 1, 181. H M.S O, London
17. Moore, R L, and Binger, C A L. (1927) *Jour exp Med.* 45, 1065
18. Polack, B., and Adams, H. (1932) *Nav. Med Bull. Wash.* 30, 165.
19. Robbins, R B (1935) *Jour Pharm exper. Therap.* 54, 426.
20. Rood, F S, and Webber, H. N (1930). "Anæsthesia and Anæsthetics" p. 124 Cassel & Co, London
21. Sise, L F (1932) *Anest & Anal* Feb p 23.
22. Thompson, J W (1931) *Staff Conf. Soper-Mills Clin.* 3, Aug.
23. Tattersall, R N (1942) Personal communication.
24. Van Allen, C M, and Lindskog, F C (1930) *Arch. Surg.* 21, 1195.
25. Waters, R M (1942) *Brit Jour. Anæsth* 1, 18.

Cardiovascular System.

1. Adriani, J. (1946). "The Chemistry of Anæsthesia." Blackwell Scientific Publications, Oxford.
2. Bayliss, W. M. (1908). *Proc. Roy. Soc. Med.* 80, 339.
3. Beattie, J., Brow, G. R., and Long, C. L. H. (1930). *J.A.M.A.* 95, 715.
4. Beecher, H. K. (1940). "The Physiology of Anesthesia." Oxford. p. 159.
5. Blalock, A. (1927). *Arch. Surg.* 15, 762.
   (1928). *Surg. Gynec. & Obst.* 46, 72.
6. Bourne, W., and Raginsky, B. B. (1935). *Amer. J. Surg.* 14, 653.
7. Derouaux, J. (1909). *Arch. int. pharmacodyn. Brux. & Paris.* 19, 63.
8. Flagg, P. J. (1922). "The Art of Anæsthesia." 3rd Ed. p. 181 Lippincott Co., London.
9. Gardner, W. J. (1946). *J.A.M.A.* 132, 572.
10. Goldschmidt, S., Ravdin, I. S., Lucke, B., Mullen, G. P., Johnson, G. G., and Ruigh, W. L. (1934). *J.A.M.A.* 102, 21.
11. Griffiths, H. W. C., and Gillies, J. (1948). *Anæsthesia.* 3, 134.
12. Guedel, A. E. (1937). "Inhalation Anesthesia." p. 51. The Macmillan Co., New York.
13. Henderson, V. E., and Kennedy, A. S. (1930). *Canad. M.A.J.* 23, 226.
14. Herrick, J. F., Essex, H. E., and Blades, E. J. (1932) *Amer. J. Physiol.* 101, 213.
15. Hewer, C. L. (1946). "Recent Advances in Anæsthesia and Analgesia." p. 31. J. & A. Churchill, London.
16. Hewer, C. L., and Belfrage, D. (1938). *Lancet.* 2, 1291.
17. Hewitt, F. W. (1922). "Anæsthetics and their Administration." p. 387. Henry Frowde and Hodder & Stoughton, London.
18. Hornabrook, R. W. (1929). *Med. J. Australasia.* 1, 629.
19. Kurtz, C. M., Bennett, J. H., & Shapiro, H. H. (1936). *J.A.M.A.* 106, 434
20. Kockmann, M (1936). "Handbuch der Experimentellen Pharmakologie Zweiter band" Julius Springer, Berlin.
21. Kennedy, W. P, and Narayana, B. (1935). *Quart J. exper. Physiol.* 24, 69.
22. Levy, A G. (1913). *Heart*, 4, 319.
23. Luckhardt, A B., and Carter, J. B., (1923). *J.A.M.A.* 80, 765.
24. Leake, C D., and Chen, M. Y. (1930) *Proc. Soc. exper. Biol. N.Y* 28, 151.
25. Mann, F C., Essex, H. E., Herrick, J F, and Baldes, E. J. (1935) *West J. Surg. Obst. & Gynec.* 43, 177.
26. Meeks, W. J. (1940) *Proc Staff Meet. Mayo Clinic*, 15, 237.
27. Meeks, W. J, Hathaway, H. R, and Orth, O S. (1937) *Jour. Pharm exper. Therap* 61, 240.
28. McCardie, W. C (1906). *Brit. med. J.* 1, 616
29. Minnett, R J, and Gillies, J "A Textbook of Anæsthetics" 6th Ed. p 195. E & S. Livingstone Ltd, Edinburgh.
30. Orth, O. S, Leigh, M D, Mellish, C. H, and Stutzman, J. W. (1939). *Jour. Pharm. exper Therap.* 67, 1.
31. Ostlere, G. (1948) *Brit. med. J.* 1, 195
32. Pilcher, J D, and Sollman, T. (1915). *J. Pharm. exper. Therap.* 6, 349, 401.
33. Parsons, F. B (1929). *Brit. med. J.* 2, 709.
34. Pohl, J (1891) *Arch. exp Path. Pharmakol.* 28, 239.
35. Rink, E. H, Helliwell, P. J., and Hutton, A. M. (1948). *Guy's Hosp. Rep* 97, 48
36. Rood, F. S, and Webber, H. N (1930). "Anæsthesia and Anæsthetics." pp. 17, 21. Cassel & Co., London.
37. Sollmann, T., "A Manual of Pharmacology." 5th Ed. W B Saunders Co., Phil
38. Veihrs, G. R. (1931) *Northwest Med* 30, 256, 322.
39. Wiggers, C J (1941) *Ann Intern. Med.* 14, 1237
40. Waters, R. M. (1936) *Lancet*, 2, 629.

41. WOODS, D. A. (1938). *Anest. & Analg.* Sept. p. 252.
42. ZIEGLER, R. F. (1948). *Johns Hopk. Hosp. Bull.* 83, 236.

The Kidneys.

1. HOGAN, (1915). "American Yearbook of Anæsthesia." p. 171.
2. MACNIDER, W. DE B. (1920) *J. Pharm. exper. Therap.* 15, 249
3. PICKFORD, M. (1947). *J. Physiol.* 106, 264.
4. STEPHENS, F (1929). *Brit. J. Anæsth.* 6, 194.
5. WRIGHT, S. (1942). "Applied Physiology." 7th Ed. p. 718. Oxford University Press, London.

The Pancreas.

1. ZUCKER, T. F., NEWBURGER, P G, and BERG, B. N. (1931) *Proc. Soc. exper. Biol. & Med.* 29, 294.

The Liver.

1. ADRIANI, J. (1946). "The Chemistry of Anæsthesia." pp 382, 383. Blackwell Scientific Publications, Oxford.
2. BLALOCK, A., and MASON, M. F. (1936) *Amer. J. Physiol.* 117, 328.
3 BOURNE, W. (1935). *J.A.M.A.* 105, 2047.
4 BOURNE, W, and SPARLING, D W. (1935) *Anesth. & Analg.* 14, 4.
5 BOICE, F (1941) "The Rôle of the Liver in Surgery." Thomas Springfield, Illinois
6 BRYAN, A W (1925). *Jour. Clin. Invest.* 2, 1.
7 CARTER, W. C, and THOMPSON, R. H. S. (1949). "Biochemistry in relation to Medicine" Longmans, Green & Co, London. p. 364.
8 COLEMAN, F. P (1938). *Surgery.* 3, 87.
9. FREW, R S (1911-12) *Proc. Roy. Soc. Med.* 5, 60.
10 GIBBERD, G. F (1935) *Guy's Hosp. Rep.* 85, 142.
11 GILLIATT, W. (1927-28). *Proc Roy Soc Med.* 21, 1136.
12. GOLDSCHMIDT, S., RAVDIN, I S., LUCKE, B., MULLEN, G. P., JOHNSON, G. G, and RUIGH, W. L (1934) *J.A.M.A.* 102, 21.
13 GOLDSCHMIDT, S, RAVDIN, I S, and LUCKE, B. (1937). *J. Pharm.* 59, 1.
14. GUTHRIE, L (1894) *Lancet* 1, 193
15. HARRIS, T A B, and MACMARTIN, R. B (1944). Unpublished.
16 HIGGINS, G, O'BRIEN, J R., STEWART, A., and WITTS, L. J. (1944). *Brit. med J* 1, 211
17 HUNTER, W (1908) *Lancet* 1, 993
18 KILLIAN, (1937) *Der Chirurg.* 7, 13, 433.
19 KING, E J, and AITKEN, R. S (1940) *Lancet.* 2, 239, 543
20 LIGHT, C, ROSS, M A, and FULTON, E (1937) *Anesth. & Analg.* 16, 167.
21. MILLER, L L, ROSS, J F., and WHIPPLE, G. H (1940). *Amer. J. Med. Sci.* 200, 739
22. MILLER, L L, and WHIPPLE, G H (1940) *Amer. J. Med. Sci.* 199, 204
23. MOLITER, H (1941) *Anesth & Analg* 20, 241.
24. PELKAN, K F., and WHIPPLE, G H (1922). *Jour. Biol. Chem* 50, 513
25. RABINOWITCH, I. M (1929) *J Biol Chem* 83, 333.
26 RAVDIN, I S, ELIASON, E L, COATES, G. M, HOLLAWAY, T B, FERGUSON, L K, GILL, A B, and COOK, T J (1937) *J.A M A* 108, 1163.
27 SHIPWAY, F E (1935) *Lancet* 1, 82.
28 STANDER, H J (1924) *Bull Johns Hopkins Hosp* 35, 46.
(1932) *Amer Jour Obst Gynec.* 23, 882.
29 SCHMIDT, C R, UNRICH, T R, and CHESNEY, V. E (1942). *Amer J Surg* 57, 42.
30. WHIPPLE, G H (1938) *Amer J Med Sci* 196, 609
(1942) *Amer J Med Sci* 203, 477
31 WHIPPLE, G H, and SPERRY, J A (1909) *Johns Hopkins Hosp Bull.* 20, 278
32 WRIGHT, G PAYLING (1948) Personal communication

The Gastro-intestinal Tract.

1. Bhatia, B. B., and Burn, J. H. (1933). *J. Physiol.* 78, 257.
2. Fine, J., Banke, B. M., Sears, J. B., and Hermanson, L. (1936). *Ann. Surg.* 103, 375.
3. Schlesinger, E. G. (1912). *Guy's Hosp. Rep.* 26, 204.
4. Waters, R. M. (1936). *Brit. med. J.* 2, 1013.

Uterus.

1. Baird, D. (1950). "Combined Textbook of Obstetrics and Gynæcology." 5th Ed. pp. 97, 135, 281. E. & S. Livingstone Ltd., Edinburgh.
2. Barcroft, J. (1946) "Researches on Pre-Natal Life." pp. 76, 270. Blackwell Scientific Publications.
3. Barton, D. H. (1946). "Researches on Pre-Natal Life." Appendix VII. Blackwell Scientific Publications.
4. Beecher, H. K. (1940). "The Physiology of Anesthesia." p 301. Oxford University Press, N.Y.
5. Blaikley, J. B., and Gibberd, G. F. (1935). *Lancet* 1, 736.
6. Bourne, A. W., and Williams, L. H. (1948). "Recent Advances in Obstetrics and Gynæcology" 7th Ed. p. 117. J. & A. Churchill, London.
7. De Lee, J. B., and Greenhill, J. P. (1947). "The Principles and Practice of Obstetrics," p 255. W. B Saunders & Co., Phil.
8. Fisher, C, Magoun, H. W., and Ransom, S. W. (1938). *Amer. J. Obst. Gynec.* 36, 1.
9. Flexner, L. B, Cowie, D. B., Hellman, L M., Wilde, W. S, and Vosburg, G. J. (1948). *Amer J. Obst Gynec.* 55, 469.
10. Galley, A. H. (1949). *Anesthesia.* 4, 154.
11. Helliwell, P. J., and Hutton, A. M. (1950). *Anesthesia.* 5, 4.
12. Hingson, J. B. (1949). *Brit med J.* 2, 777.
13. Malkin, C. M (1947). *Proc Roy soc Med* 60, 577.
14. Marshall, C. M. (1947). *Proc Roy soc. Med.* 60, 577
15. Organe, G. S. W. (1950) *Brit med J.* 2, 277.
16. Resnick, L. (1945) *Brit med J* 2 722
17. Reynolds, S. M R (1939) "The Physiology of the Uterus." Hoeber, N.Y.
18. Roos, J., and Romijn, C (1938). *J. Physiol.* 92, 249.
19. Thomas, R. H. (1947). *Proc. Roy. soc Med* 60, 577
20. Thomson, K J., Kirshiemer, A, Ginson, J. G., and Evans, W. A. (1938). *Amer. J. Obst. Gynec* 36, 48.
21. Weintraub, F., and Merrian, M S. (1943). *Amer J. Obst Gynec.* 46, 6.
22. Wright, H. Patling, Osborne, S. B., and Edmonds, D. G. (1950). *Surg. Gynec. Obst.* 90, 481
23. Wright, S. (1942) "Applied Physiology" 7th Ed p 280. Oxford University Press.

Body Temperature.

1. Bazett, H. C., Love, L., Newton, M., Eisenberg, L., Day, R., and Forster, R (1948) *Applied Physiol* 1, 1.
2. Benedict, F. G. (1915). *Carnegie Inst. Washington Pub.* 203.
3. Burns, D. (1921). "An Introduction to Biophysics" p 348. Churchill, London.
4. Davis, S. G (1909) *John Hopkins Hosp. Bull.* 20, 118.
5. Moore, L M. (1918) *Amer J. Physiol.* 46, 244, 253.
6. Swift, R. W. (1932). *J. Nutrition.* 5, 213, 227.
7. Wright, S. (1942). "Applied Physiology." 7th Ed. p. 594 Oxford University Press

Anæsthetic Explosions.

1. Adriani, J. (1946). "The Chemistry of Anæsthesia." p. 301. Blackwell Scientific Publications, Oxford.
2. Chivers, E. H. (1943). *Lancet* i, 527.
3. Cheney, M. B., and Folkman, M. L. (1930). *Anesth. & Analg.* 9, 11.
4. Epstein, H. G. (1944). *Lancet.* I, 114.
5. Guedel, A. G. (1937). "Inhalation Anesthesia." pp. 143, 153, 155, 163. The Macmillan Co., New York.
6. Horton, J. W. (1941) *Anesthesiology.* 2, 121.
7. Ironside, R. (1935). *Proc. Roy. soc. Med.* March 1st.
8 Rayner, E. H. (1938) *Proc. Inst. Elext. Engin.* Feb.
9. Rovenstine, E. A. (1936) *Amer. J. Surg.* Dec. 460
10. Stead, G. (1945). Personal communication.
11. Townend, D. T. A., and Chamberlain, E. A. C. (1936). *Proc. roy Soc. Lond.* 154, 95.
(1937). *Proc. roy. Soc. Lond.* 158, 415.
12. Woodbridge, P. D. (1939). *J.A.M.A.* 113, 2308.

INDEX